EXHIBIT AA

COMMONWEALTH OF MASSACHUSETTS

MIDDLESEX, ss: SUPERIOR COURT DEPARTMENT
OF THE TRIAL COURT

****

MARIA CARDENAS,

Plaintiff,

v. Civil No.
MICV2012-02912

BOSTON SCIENTIFIC CORP.,
(d/b/a MANSFIELD SCIENTIFIC,
INC. & MICROVASIVE, INC.),
and JOHN DOE CORPORATIONS
1-50,

Defendants.

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TRIAL

BEFORE: The Hon. Diane M. Kottmyer

Monday, August 18th, 2014

8:45 a.m.

Held At:

Middlesex Superior Court
200 Trade Center
Woburn, Massachusetts

REPORTED BY:

Maureen O'Connor Pollard, RMR, CLR, CSR #149108

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PROCEEDINGS

THE CLERK: Court, all rise, please. Please be seated. Court is now in session.

THE COURT: Good morning. You wanted to be heard?

MR. OSBORNE: Yes, your Honor.

Where we concluded Friday relative to the deposition of Maya Matusovsky, the parties have gotten together, going through your order relative to the testimony and to the exhibits, there's one section we're a little unclear on.

THE COURT: Of course.

MR. OSBORNE: There's -- the section has to deal with two exhibits you've testified come in, and we want to play the testimony that goes along with that, with those two exhibits. So I just want to show them quickly to your Honor --

THE COURT: Of course.

MR. OSBORNE: -- with the exhibits. Here's the two exhibits. And I've marked the testimony off, your Honor, in this transcript.

MR. ANIELAK: Your Honor, before you

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glance through the exhibits, let me just put one little short context.

When you went through the page and line of the deposition, there were portions where you excluded it as being redundant and repetitive, and these documents were part of that portion. Basically it's just reiterating the same thing. So that's what's going on here.

THE COURT: I see.

MR. OSBORNE: Your Honor, I would just add that --

THE COURT: And this is at the tabbed page, is that correct?

MR. OSBORNE: Correct.

THE COURT: Let me just look at it.

That's all admissible, that portion.

MR. OSBORNE: Thank you, Judge.

MR. ANIELAK: Your Honor, the issue, though, was in terms of hitting the same -- those same points are made in the PowerPoint. So we're going through the same thing three times, and that was your Honor's ruling on the deposition designations.

THE COURT: The documents are

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admissible, and so consequently the testimony relating to the documents is admissible, otherwise it would -- the documents themselves would stand alone without any explanatory testimony.

MR. OSBORNE: Just some quick guidance from the Court on the Sling City contest. The last two pages have to do with the prizes that you ruled come into evidence. Mr. Anielak has a problem with the pictures that are associated with it.

THE COURT: May I see it again, please? I'm sure I have it here.

MR. OSBORNE: We've come to agreement on all the slides, just the last couple slides he has an issue with, the bag of money, the picture of Monte Carlo. As to whether or not those should be taken out, I was wanting the Court's guidance on it.

MR. ANIELAK: I don't think they have any probative value, your Honor.

MR. OSBORNE: They are the slide, it's really what the contest had to do with. And if you prevailed, what the prizes were, which has

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already been ruled upon, so I don't understand what the difference is, but...

THE COURT: Is there something else that identifies the trip? There is, isn't there something else that's admissible that identifies the trip as being to Monte Carlo?

MR. OSBORNE: Yes, your Honor.

MR. ANIELAK: The document you just admitted.

THE COURT: All right. All right. And is there something else that identifies the amount, the prize amount?

MR. OSBORNE: Yes, your Honor.

THE COURT: Then it's all cumulative, so it's excluded.

MR. OSBORNE: Okay.

THE COURT: Thank you.

MR. OSBORNE: Thank you, Judge.

MR. MONSOUR: Your Honor, one other point.

We're going to call Dr. Guelcher first, your Honor.

THE COURT: Yes.

MR. MONSOUR: You've seen him before,

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he's the polypropylene expert from Vanderbilt.
THE COURT: Yes. And I think I have his deposition here.
MR. MONSOUR: And Dr. Guelcher, our testimony with him is going to be relatively brief.
I've just been advised by Mr. Anielak -- I sent him a list of what I plan on using with Dr. Guelcher. It's very short. The documents that I want to use with him are two MSDS sheets, one is on the approved list, one is not on the approved list, but Mr. Anielak has agreed to its admissibility.
And the other is the document that I showed in opening, the C.P. Chem document talking about bio -- degradation and embrittlement, I want to show him that document. Basically my direct is going to include those three documents, potentially two others. Mr. Anielak has objected to me using those.
I'm going to offer these documents into evidence before Dr. Guelcher gets on the stand. So they are all agreeable to the Defendant, and pursuant to 703 of the proposed

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rules, it says evidence -- experts can testify to evidence that's already in the record or that will be presented during the course of the proceedings. And so I would like to be able to use those.
THE COURT: What would you have him do? In other words, once a document is in evidence, any witness can read from the document, or attorney for that matter, if the document is in evidence.
MR. MONSOUR: That's all I'm going to do. I'm going to show him --
THE COURT: That's permissible.
MR. MONSOUR: Okay. Thank you, your Honor.
MR. ANIELAK: If he's going to ask him opinions about it, those have not been disclosed in the disclosure. The documents that were unsigned --
THE COURT: He hasn't indicated he's going to ask opinions. He can show him the document and ask him to read from the document, identifying what it is for the record, if it's in evidence.

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MR. ANIELAK: Okay, your Honor.
MS. MURPHY: I just wanted to take a minute to update the Court as to where we think we are scheduling-wise.
I think the Plaintiffs expect to move fairly quickly today and get a fair amount of evidence in. My understanding is that tomorrow there may be another deposition or two --
MR. MONSOUR: Here's what we think. We never know how long -- all we know is how long our directs we think are going to be. So with that caveat in mind, having read Mr. Strongman's cross examination of Dr. Guelcher from the first trial, and knowing that I will not go into as much with Dr. Guelcher, I expect Dr. Guelcher's direct and cross to be shorter than in Albright. I cannot remember how long he was on the stand in Albright, I think it was about two-and-a-half, three hours.
THE COURT: If you tell me where you think you're going to be, I'm not going to hold you to it.
MR. MONSOUR: Okay. Okay.

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THE COURT: I understand that these are all estimates.
MR. MONSOUR: All estimates.
THE COURT: Where do you think you will be?
MR. MONSOUR: We think we will get through Dr. Guelcher and Dr. Iakovlev, through direct and cross today, and we might even give the Court back some time, or we might move on to playing one of these -- this is why we were working on the Matusovsky depo, because we think it's possible we get through both of these and we have some time at the end of the day to play Matusovsky.
THE COURT: Okay.
MR. MONSOUR: That's our best estimate. It's ambitious, but we can do it, we think.
THE COURT: And then tomorrow?
MR. MONSOUR: Tomorrow we're going to call Doreen Rao. And we're going to -- are we going to call --
MR. OSBORNE: The Plaintiff.
MR. MONSOUR: The Plaintiff. And then

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potentially Lee Sullivan.
MR. OSBORNE: Lee Sullivan today, hopefully, if we can get to her. Lee Sullivan today or tomorrow.
MR. MONSOUR: By video.
MR. KEENAN: By video.
MR. MONSOUR: By video. And then potentially another corporate witness from Boston Scientific either tomorrow or the next day to be Rob Miragliuolo. But we need to talk about that -- probably talk about that tonight or tomorrow night.
MS. MURPHY: So ambitiously, I must admit, but there's a possibility that the Plaintiffs will finish their evidence at some point Wednesday, and we would anticipate starting to call witnesses on Wednesday afternoon, and we have an expert scheduled for Wednesday to come in. And then on Thursday we would have -- we're still shuffling, but we think that all but one witness could be completed this week.
The problem that we may encounter is Friday, and not having a witness scheduled for

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Friday.
THE COURT: Well, let me ask you a question. If I tell the jurors that they're going to have Friday off, is there some witness that you have scheduled for Thursday that if we don't finish that you need to call on Friday?
MS. MURPHY: I would doubt it. But I would ask that the Court not alert the jury until -- certainly until we complete tomorrow and get a better handle as to where we are.
THE COURT: All right.
MS. MURPHY: But I just wanted to let the Court know that that was a possibility.
THE COURT: I think that that's an option, because I think the jurors would appreciate having a day off, and I would rather excuse them for an entire day than have a lot -- have several short days.
MS. MURPHY: Right.
THE COURT: So if you can review what you have so that tomorrow I can tell them so that they can plan for having the day off.
MS. MURPHY: Yes.
And then I thought that would give us

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an opportunity, as we did before, to review the charge and directed verdict business and all of that.
THE COURT: Yes.
MS. MURPHY: Okay.
THE COURT: All right.
MR. ANIELAK: Your Honor, we filed and served over the weekend the gold standard/standard of care brief with a number of attachments, and we provided copies to the Plaintiffs.
THE COURT: All right. I just got that. I haven't reviewed it yet.
When do you anticipate you'll get to that; with your witnesses?
MR. ANIELAK: Yes.
THE COURT: All right. So today is Drs. Guelcher and Iakovlev?
MR. OSBORNE: That's correct, your Honor.
THE COURT: I just want to pull out, I know I have copies of their materials.
MR. ANIELAK: Your Honor, we have a notebook that has additional materials in it

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that you may need, so I have it all in one place if you like.
THE COURT: I may need for this?
MR. ANIELAK: For Dr. Guelcher.
THE COURT: For Dr. Guelcher, oh, thank you.
As soon as the clerk comes back, you can hand it to the clerk.
I take it that all of the jurors aren't in yet, otherwise Officer Serra would be in the courtroom.
MS. MURPHY: Your Honor, for use a little bit later, I didn't know the timing, this is all the materials for Dr. Iakovlev, 26(b)(4) deposition, etcetera (handing).
THE COURT: Thank you.
Are all the jurors in yet?
THE CLERK: They're all in, your Honor.
THE COURT: All right. And is the witness in the courtroom?
MR. OSBORNE: No, your Honor.
THE COURT: The other thing I wanted to mention, there's an individual here from a

media -- a registered media outlet who wishes to record the proceedings. And he's complied with the rules, so he will be permitted to do that for publication on a webcast, subject, of course, to the rules of the Supreme Judicial Court's Rule 1.19.

He will set up his equipment at lunchtime. And the best place for him to do it -- he's not permitted to record the jurors -- the best place for him to do it is apparently where Ms. Cardenas is sitting. And I don't want to interfere with her ability to see the witness and participate, so would you mind, during the break, reviewing with him how much equipment he has, where it would be, and letting me know if that would affect Ms. Cardenas's location?

MR. OSBORNE: Sure. No problem.

THE COURT: Thank you.

MR. OSBORNE: One other housekeeping issue, Judge.

During Dr. Iakovlev's testimony, he has a microscope that he wants to put the slides under and project up to the jury on a couple different points. Do you have any preference

where you would prefer the microscope to be set up?

THE COURT: No. So long as it doesn't interfere with anyone's view. But, Counsel, if you can't see, you can get up and move around. And obviously the jurors have to be able to come in and go out.

MR. OSBORNE: Sure. I'll work with the technical guys to make sure it's set up and it's convenient for the Court.

THE COURT: All right. Is the witness in the courtroom?

MR. MONSOUR: He's right outside the door. Let me get him.

THE COURT: Okay. Thank you.

(Pause.)

THE COURT OFFICER: All rise. Jury entering.

(Jury present.)

THE COURT OFFICER: Court is in session. You may be seated.

THE COURT: Good morning, ladies and gentlemen.

A couple of things. First, before

beginning, let me just ask; has any juror discussed the subject matter of the case with anyone, done any independent investigation concerning the case outside the courtroom or anyone involved in the case, or heard or read anything outside the courtroom that could affect your ability to be fair? If so, please raise your hand. No.

All right. And I'm sure the jurors are wondering whether we're on schedule or where we stand, and we are very much on schedule, so you needn't be concerned that we're falling behind.

So with that, is it Mr. Osborne or Mr. Monsour?

MR. MONSOUR: It's me, your Honor.

Your Honor, at this point, we would call Dr. Scott Guelcher to the stand.

THE COURT: Dr. Guelcher, please come forward.

THE COURT OFFICER: Stop right here, please. Face the clerk, raise your right hand.

SCOTT A. GUELCHER, PhD,

having been first duly sworn, was examined and testified as follows:

DIRECT EXAMINATION

BY MR. MONSOUR:

Q. Good morning.

A. Good morning.

Q. Would you please introduce yourself to the ladies and gentlemen of the jury?

A. My name is Scott Guelcher. I'm associate professor of chemical engineering at Vanderbilt University in Nashville, Tennessee.

MR. MONSOUR: Okay. If we could, would you go ahead and put up the PowerPoint?

BY MR. MONSOUR:

Q. Dr. Guelcher, what I'd like to do is to give the jury a little idea what we're going to talk about. I want to introduce you, talk about your background, and then we'll go through some of the -- I'm going to go through some of the opinions that you have today. Okay?

A. Yes.

Q. All right. First off, let's talk about your educational background, if we could.

A. So I have a Ph.D in chemical

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engineering from Carnegie Mellon University. Also done a post-doctoral fellowship in biomedical engineering at Carnegie Mellon.

My current position, I'm associate professor of chemical engineering and also biomedical engineering. I have an appointment there as well.

I have authored over 50 peer-reviewed articles. I've edited a textbook on biomaterials, written a number of book chapters on biomaterials. I'm member of a number of professional societies, including American Institute for Chemical Engineers, Society of Biomaterials, and American Chemical Society.

Q. And you speak frequently around the world, is that a fair statement?

A. Yes. My students and I give talks at scientific meetings regularly, national and international meetings.

Q. Okay. And in the near future do you have any international meetings, speaking engagements planned?

A. I'm traveling to China for an invited talk on 3D printing of scaffolds for

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regenerative medicine.

THE COURT: Sir, if you could, just slow down a bit and keep your voice up. The microphone, you might want to move that a little bit to the left to be sure it's picking up your choice. Thank you.

THE WITNESS: Okay.

BY MR. MONSOUR:

Q. In your work as an engineer, as a professor, you've received grants, haven't you?

A. Yes.

Q. And could you give us an idea of the nature of those grants and what they're for?

A. So I've received several grants from the National Institutes of Health. These are looking at problems such as trying to understand cancer metastasis to bone, what causes this, how can we treat it. I have grants directed toward developing weightbearing bone grafts for different types of fractures, where we're trying to make a bone graft that will stabilize a fracture and heal at the same time, which is challenging to do. Grants looking at how to treat infection in bone; so how do I heal bone

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that's infected with bacteria. And then also a grant on wound healing, so trying to design different grafts for helping wounds heal better, especially in patients that don't heal well.

Q. Okay. I notice that you've got -- some of your grants are from the Department of Defense, and I think it's Armed Forces something?

A. Yeah. So that's the Armed Forces Institute of Regenerative Medicine. That's a multi-institutional program, there's about 20 universities involved in this. And the idea is to really be able to find new therapies to treat soldiers that have been injured in the wars, so focusing on every part of the body from limb salvage.

My particular area is in craniofacial regeneration, so we're trying to reconstruct the mandible. Soldiers who have lost their mandible from either bullets or explosions, trying to rebuild that mandible, so we can restore teeth, and then they can have dentition again and have a more productive and better life.

Q. Okay. Let's talk a little bit about

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your background.

You have not always been in academia, correct?

A. No. I've moved some, worked in industry as well. So I started after college, worked at Eastman Chemical for two years in their polymers business. So we looked at polyesters and nutritional supplement products when I was working there.

Then I went and did my Ph.D at Carnegie Mellon.

And after that, I worked at Bayer Material Science for three years in their polyurethanes division, so that was all different types of chemicals used to make polyurethanes, including things that we call polyols, polymer fill polyols. And these were all hydrolytically stable polymers that you would use, say, in seat cushions and things like this. So that's my industrial experience.

And then at Vanderbilt, I focused mostly on design of basically degradable materials for tissue regeneration.

Q. Okay. So since you've been at

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Vanderbilt, kind of give us an idea of some of the various things that you've been working on there.

A. So when I started -- in my post-doc at Carnegie Mellon, I extended a lot of the work I'd done at Bayer on polyurethanes that were biostable materials to looking at biodegradable materials. So you have to make a lot of changes in the chemistry. So we make these from amino acids. And it turns out they have very nice degradation properties and we can use them as tissue grafts.

Then at Vanderbilt, I've expanded that work where we started off with polyester urethanes that will degrade by water, so you put them in water and they degrade. And this is kind of not such a smart degradation, it just reacts with water and degrades. And since then, we've moved into what we call smart degradable polymers, which would be these polythio t-cell urethanes. And these degrade in response to oxidation, so cells in the body secrete reactive oxygen species that degrade these polymers. And so the advantage there is that they basically

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degrade at the rate at which new cells grow in, so you can have much better control over -- in a patient that doesn't heal as well. Maybe the polymer in the middle could degrade, you could end up with a hole. But with these smart degrading polymers, we have much more control over the rate at which they degrade.

So we see these as kind of the next generation, more favorable way to try to heal the body, especially in wounds that don't heal.

Q. Okay. I want you to explain what you just said in an example that's a little bit easier for me to understand. Give me an example of how you're working with body decomposition, things are building in the body. Give us an example of how you're working to build things that will help the human body.

A. So what we generally try to do is -- our general approach is to inject a material as a liquid, so it's easy to inject. You can handle it very easily in a syringe, you inject it, and then in the body it cures to form a solid, what we call a scaffold. So this scaffold, cells can grow into it, they migrate

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onto the scaffold and they deposit new tissue.

That's great, but at the same time, you want that scaffold to go away. You want the new tissue to replace it, because if it stays around it can cause an infection or some problems. So we design these scaffolds that actually degrade in response to the cells that migrate in. So the cells migrate in, they deposit new tissue, they secrete species that cause the scaffold to degrade, and by the end of four to six months, or maybe longer if it's a large defect, you've replaced that defect with new tissue, the scaffold is gone, and you basically heal the patient. That's the goal of what we're trying to do.

Q. Okay. So you put the scaffold in. As the bone is growing into it, the scaffold degrades, and by the end you've got a new bone, and whatever was giving it structure has basically disintegrated into the body?

A. Is gone. That's right.

Q. Okay. Let's look at some of your industrial experience. We've kind of gone over this a little bit.

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You worked at Eastman, you worked at Bayer. You've been a consultant for several companies over the years, haven't you?

A. Yes.

Q. Can you give us some example of some consulting work you've done?

A. So the first consulting work I did was at Eastman. I worked there for a few years, and then after I left they still wanted me to help with this project we were working on. So I worked for two to three years on a part-time basis as a consultant, finishing that work up.

I've also done some consulting work, some materials answers where they -- that was a Plaintiff's case in looking at defective automotive coatings.

McLane law firm was a defense litigation where I was essentially defending the polyurethane manufacturer against some claims.

And then Polymer and Chemical Technologies is the company of Russell Dunn that I'm working for now in this litigation.

Q. Russell Dunn is another professor at Vanderbilt?

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A. He's the professor that practices at Vanderbilt that I work with.
Q. Okay. Is he a good engineer?
A. Yes.
Q. Okay.
A. He has a lot of industrial experience, which is good for our students.
Q. Okay. You talk about some of the academic industrial partnerships that you've been in, the bone grafts. Is that what you were just talking about?
A. Yes. So a lot of the work that -- I like doing basic research. But one exciting thing about this field is the opportunity to translate technology. In fact, the DOD really expects it of us. So the idea is you can do something in the lab, but what we really want to do is translate that and actually make people's lives better.
So one example would be the bone grafts that we're designing with a major biomedical device manufacturer where we're trying to basically make grafts that will do things other grafts won't do; weightbearing

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cements that can hold bone together, give it strength while it's healing.
We're also looking at injectable dressings for low-pressure wound therapy. So this would be, you know, a bad wound, a lot of times they'll put a wound vac on it to sort of draw the exudate out. And we're -- the problem with these things is when you take the wound vac off and the dressing off, it's affixed to the skin, so it's like ripping off a really painful Band-Aid. So we're looking at problems like making an inner layer that will degrade. So after a few weeks, that inner layer is gone, it will be a lot easier to take the wound vac off. And so there's two major device companies I'm working with.
And my students also started a start-up company that we're working with on some of these technologies as well.
Q. And if we look kind of at the bottom of the sheet, it talks about chemical engineering practice, student professional development at Vanderbilt. What do you do in that capacity?

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A. So as a professor, we -- you know, part of our mission, the very important part of our mission is training students. So we like to take a lot of what we learn in the real world, from either consulting cases or design of technology, and imparting this to our students; how do you make ethical decisions, how do you handle decisions that might be difficult to make when you're working in industry. So this is what we call professional practice, helping students understand what they want to do next in life, and how they can behave responsibly and ethically as an engineer, which is an important part of our training.
Q. Okay. You've reached some -- or you've formed some conclusions and you've got some opinions about this case, correct?
A. Yes.
Q. And are those opinions held by you to a reasonable degree of scientific and engineering certainty?
A. Yes.
Q. Okay. Let's look at some of those opinions. What is your first opinion in this

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case?
A. So the first opinion states that "Polypropylene is not inert."
Q. Okay. What does "polypropylene is not inert" mean?
A. So I believe that the body of the scientific literature and the evidence I've seen points to the fact that, upon implantation, polypropylene will react with the human body and its properties change. That's essentially what that opinion means.
Q. And over time, what will happen to it?
A. So as the properties change, it will become brittle. So it starts off as a flexible ductal material that you can stretch easily. Over time, it becomes brittle and hard due to these changes that I'll talk about.
Q. All right. Okay. Your next opinion, "Antioxidants within the Obtryx (Advantage) mesh do not last forever." Is that one of your opinions?
A. That's of my opinions. And antioxidants are commonly added to protect materials, but it's typically for a certain

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period of time. So it's not forever. Eventually, those antioxidants will be depleted, and these changes will start to occur.

Q. Okay. The third opinion, "When antioxidants are depleted, the mesh reacts with oxygen, causing it to become brittle and stiff." Tell me why that happens.

A. Well, once the antioxidants are depleted, there's nothing to scavenge the radicals, the peroxides. And so the only thing that these oxygen species can react with now is the material itself, because the antioxidants that protect it are gone. So when the antioxidants are depleted, these reactions will become important and material properties will change.

Q. If we look at your fourth opinion, "When the Obtryx (Advantage) mesh is implanted, a foreign body response occurs." What does that mean?

A. So it's been well-known since the 1990s that there's a foreign body reaction or a foreign body response to an implanted biomaterial. And the material is colonized by

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cells, inflammatory cells, that respond to that material, and can be stimulated to secrete certain species, certain compounds, that will react with the material. And so the big question is, how does the material respond to these things that are secreted by the cells. That's a very important question when you're looking at designing a biomaterial or selecting a biomaterial for an application.

Q. All right. What's your next opinion?

A. Number 5 is the body will stop responding to the mesh until it's entirely removed.

Q. Will not stop?

A. I read that incorrectly. "The body will not stop responding to the mesh until it's entirely removed."

Q. Okay.

A. So this process is ongoing. It doesn't stop until either the body destroys it, pushes it out, like a splinter would be extruded. It's either destroyed, it's extruded, or the body is just going to continue.

Now, in our case, with some of the

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materials we're designing, we want this to happen. The material is designed to degrade in response to this, so it would be replaced by host tissue. But if you're dealing with a biostable implant, something that's supposed to last for the life of the patient, that's a very different problem. And in this case, you don't want it to degrade. You don't -- but this response, this reaction from the body, will continue as long as it's there.

Q. Okay. Your sixth opinion, what does that mean?

A. So when I say that "Less mesh is better," this really comes from opinion 5, in that we know that this response from the body is continuing, so if you have more surface area, if you have more mesh, you're going to get more response. If you have less mesh, you're going to have less response. It's just a fact that this is a surface-driven problem. The surface is covered with these cells.

Q. Okay. Seventh opinion, "The effects of oxidation on polypropylene's stability have long been known." What do you mean by that?

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A. So when engineers are first looking at using polypropylene, it was noted pretty quickly that it degrades rapidly in the presence of oxygen. And this was all worked out in the 1960s, and this is what led to the use of antioxidants to extend the service life of the polypropylene. But this chemistry was worked out really in the 1960s.

Q. Okay. Well known in the scientific community?

A. Yes.

Q. For quite some time?

A. Yes.

Q. Okay. And your final opinion in the case is, "Boston Scientific did not establish the non-reactivity of the Obtryx (Advantage) mesh with strong oxidizing agents," correct?

A. Yes, that's right.

Q. Why would that be important to do?

A. Well, when you're selecting a biomaterial for an implant, you have to really understand how that material reacts with the body, with the environment. And that's something that would have to be looked at. You

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would have to -- so we know that the foreign body reaction is going to happen, it's going to be populated by cells, you're going to get cells all over the surface of the material. And really the important question, from an engineer's perspective, is how does the material respond to that.

So these cells are going to do what they do, they secrete these different species that will oxidize it, acids, etcetera. And the question is, how does the material respond to that? That's a very important question.

Q. Okay. We'll go to the next page.

Could you explain to us the different types of polymers that can be implanted in the human body?

A. So throughout my career, I've worked on a number of these different polymers. And I tried to break it down into really the different classes of materials that have been investigated.

So the first would be "Hydrophobic - No Hydrolyzable Bonds." What that means is that if it's hydrophobic, that means water doesn't

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like it. So it doesn't swell with water. If you put it in water, its shape doesn't change.

"No hydrolyzable bonds," that means that there's no bonds in the material that react with water and break down. So you would theorize that this would be a very stable material if you don't consider, basically, the effects of the human body.

Now, the next one is "Hydrophilic - No Hydrolyzable Bonds." So, again, if it's hydrophilic, that means it likes water. So it's going to absorb a lot of water, its volume, its shape is all going to change when you put it in water. But it still doesn't have any hydrolyzable bonds. That means it's not going to react with the water. So it will swell, increase its volume, shape, but it's not going to degrade.

Now, the next one would be what's called a hydrophobic material with hydrolyzable bonds.

You want to maybe go to the next slide that has the red box.

Q. Sure.

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A. So just to highlight some of the work, so these hydrophobic hydrolyzable materials, these are the materials, the first-generation scaffolds that I've been working with, where they're hydrophobic, so they don't absorb water. They maintain their initial properties. But they're hydrolyzable, that means they'll react with water in the body and begin to break down.

And so this is kind of an uncontrolled degradation, right? It's just once you put it in, from the center of the material to the outside, wherever there is water, it's going to react and the material is going to break down.

Now, the problem is, is like I was saying earlier, the cells take a very long time to get to the middle. And the scaffold is gone, it doesn't help, right? It doesn't do you any good. So for very large defects, this is a problem.

So that's why we've been moving to this system, the next one, which would be "Hydrophobic with cell degradable bonds." So these are materials that are also, again, hydrophobic. They don't absorb water. But they

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have bonds and then they can broken down by cells in response to, say, reactive oxygen secreted by cells.

So we're sort of designing materials to respond to this foreign body reaction in the way that we want. In other words, we want the scaffold to go away as we have new tissue growing in. And it's all mediated by the cells. So we think this is a much safer approach for some types of tissue scaffolds.

And the last one would be "Hydrophilic - Hydrolyzable Bonds." These materials aren't used a whole lot in scaffolds, because they absorb water. When they absorb water, they degrade. So they can go away very, very fast. So you might use something like this for a drug delivery system. You just want to deliver a drug for a week, you put it in and it goes away, delivers the drug.

So these would be the several different types of materials that can be implanted in the human body, these, essentially, five groups.

Q. All right. Let's go on to your next

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slide. Talk about this, "Smart degradation of tissue-engineered grafts."

A. So, again, this is a comparison of sort of the traditional hydrolytic degradation versus what we call smart degradation. So in hydrolytic degradation, it results from water. So it's ester bonds, for example, that are very reactive with water. Degradation starts upon implantation, so like I was saying, once you place that graft, even if it's a very large defect and you place that graft and the scaffold in the middle starts to degrade, as well as the scaffold on the outside.

And so what this can lead to, you know that cells are coming in from the outside-in, so if the scaffold degrades before the cells get there, you have a hole. And we've seen this in some of our studies where you just have a large hole in the center and it didn't heal well.

Now, with cell-mediated degradation, we can basically -- in here, degradation comes from enzymes that are secreted by the cells, either oxidative or proteolytic. So the cells -- this is sort of designing an implant to

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take advantage of this foreign body reaction. So we're designing the material to degrade in response to this foreign body reaction. And degradation doesn't start until the cells migrate in. So in the center, we see no degradation until the cells get there. And in this way, we can match degradation and tissue growth and end up with something that heals much more reliably. That's the difference.

Q. Let me ask you this.

Is it a fair statement to say that you spend a lot of time studying the foreign body reaction to devices that are implanted in the body?

A. Yes. This is a difficult -- I mean, I explained it in this way, but it's very difficult to get it to work. So we have to think a lot about what types of cells are there, we have to characterize the cells, what exactly are they doing, the rates at which these processes occur. So there's a lot of backstory behind this that we have to look at very carefully.

Q. Okay. Let's talk about polypropylene.

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Ms. Cardenas had an Obtryx device implanted in her that was made out of Marlex polypropylene. Could you tell us what Marlex -- or what polypropylene is?

MR. ANIELAK: Object to the form, your Honor. Object to the introduction about Marlex mesh.

THE COURT: The objection is overruled. The question for the witness had to do with polypropylene.

Could you tell us what polypropylene is?

THE WITNESS: So polypropylene is what we would call a synthetic or a manmade material. It's derived from petroleum feedstocks, so it's a petrochemical-based material. It's produced in pellets. And as I was saying earlier, it's known to be unstable, it oxidatively degrades due to its molecular structure, so this is just intrinsic to the structure of the molecule.

Q. Back to your chart, if we look to your chart of different types of polymers, polypropylene turns out to be in the first group that originally was thought to be most stable in

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the '70s, correct?

A. That's right. So in the '60s and '70s, polypropylene has good chemical resistance in a number of areas, so there was some enthusiasm for using this as a biomedical implant, because, as I was saying, it's hydrophobic, it doesn't hydrolyze. So if you look at this from this perspective, without really considering the effects of the foreign body reaction, which wasn't known at that time, it looks like it would be a good idea to implant this material.

Q. And you've got a comment down here, it says, "But the physiological environment cannot be modelled as a simple saline solution."

What does that mean?

A. Well, we know that the body environment is much more complicated than just physiological fluid. There are these cells, like I was saying, that colonize and attach to the surface of the implant after it's implanted. And so we can't model this just as saline, some kind of physiological saline solution. It's much more complicated. But a lot of this wasn't

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known at the time, '60s and '70s, it wasn't -- hadn't been worked out.

Q. So to test polypropylene, you would want to do more than stick it in saltwater or a saline solution?

A. Yes.

Q. "Oxidation of polypropylene (1960s)." Tell us what this is about.

A. Okay. So the mechanism is very complex, and what I tried to do here is summarize and hit the important features of this and why it matters.

So the structure of polypropylene is shown on the left. And you see there's a hydrogen atom with a little red box around it. Well, that's what's called a tertiary carbon hydrogen bond. And it's that bond that makes polypropylene susceptible to oxidation. That's the key to the whole idea.

So, in this case, this was worked out in the 1960s in the presence of heat and molecular oxygen. That's just oxygen in the air that we breathe. There's a series of reactions that can occur.

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And you can see the first one I've shown is a very important intermediate, that's called a hydroperoxide. So that's COOH. And then there's that OH group with the bond around it -- with, I'm sorry, a red box around it. That's a hydroperoxide group, that COOH.

And that can be detected using a number of methods. People have used what's called foray transform, infrared spectroscopy. That's a spectroscopy method for detecting it. You can also use more advanced surface methods that are available today.

And then finally what will happen is that chain will break. And so you see the arrow pointing down to the second row, and this is called chain scission. So the polypropylene is a very, very long chain, like a piece of rope. And you can imagine just cutting it, cutting little pieces of it off. And this will result in what's called a carbonyl, which is that CO group that can also be measured by FTR. And the other -- and then also a free radical. So this one on the right, you can see that little black dot, that's a free radical.

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And that free radical can propagate this reaction further. So this reaction just continues until the polypropylene is broken down into very small segments. That's what we call the molecular weight, the weight of one long molecule.

Q. Okay. So let's look at this next slide entitled "The Oxidation of Polypropylene." And I notice at the top you've got -- part of the slide says "Induction" and the other part says "Degradation." Could you tell us what this slide means?

A. So this is a -- kind of a simplified graph summarizing what's known about this.

So on the Y axis, on the axis going up, this is change in properties. So this change in properties could be concentration of reactive groups that you can measure. It can be loss in molecular weight. It can be mechanical properties. So this is the change in properties. And we're looking how they change with time.

And there's two stages of this. So the one on the left is called Induction. So

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during the induction period, the changes are very slow and very small. During this period, you can be consuming any antioxidant that's added. And there's a slow increase in these carbonyl and peroxide groups that I showed in the previous slide. You see a very kind of slow increase in these groups that tells you the reaction is going, but it's rather slow.

At some point, we hit this induction time, where the reaction becomes much faster, because you have enough of these groups.

Q. That right there?

A. Yeah, that's the induction time. Sorry. Where the slope is -- yeah, this hockey stick plot that everybody is familiar with from global warming, right? So it's the same idea. Catastrophe sets in when you -- when you see this very high slope, this is what we would call a degradation. And this, we have a rapid increase in these reaction products that you can measure by spectroscopy. We see a reduction in molecular weight, that is the chain being broken down into many smaller changes. And this causes problems like embrittlement. So it goes from

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being soft and complaint, stretchy, to something that's hard and rigid and brittle. It can lead to mechanical failure, to cracking, pieces of it can sluff off and cause problems.

So this is the concept of, basically, when it's exposed to oxidizing agents, polypropylene's properties will change with time, and this is the way that that happens.

Q. Okay. And as a result of the oxidation of polypropylene, as you said before, it degrades, it becomes brittle and hard, and there's mechanical failure of the products, correct?

A. That's right.

Q. Now, if we look at your next slide, it says "Polypropylene is easily oxidized." Is that something that's generally accepted in the medical community -- I mean in the engineering community?

A. Yes. This is well known that polypropylene is more susceptible to oxidation than a lot, so low -- a lot of other materials. So low density, high density polyethylene, this is used in things like plastic milk jugs, things

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like that. Nylon.

THE COURT: I'm sorry, I didn't understand what you just said, the words. Could you repeat that?

THE WITNESS: Oh. The low density polyethylene is used in milk packaging, nylon, which I think most of us are familiar with this, carpet fibers. And then some of these fluorinated polymers are very resistant to oxidation.

So what I really just wanted to show here is that polypropylene is one of the more easily oxidized materials that's out there, compared to a lot of others.

BY MR. MONSOUR:

Q. Fair enough.

Now, "In vivo degradation of unstabilized polypropylene (1970s)." Let's break this down first.

What does in vivo mean?

A. So when we say -- we can talk about in vitro, which is outside the body. Vivo is inside the body. So experiments that were done with polypropylene inside the body.

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Q. Okay. And then it mentions here "Degradation of unstabilized polypropylene."

What's unstabilized polypropylene versus stabilized polypropylene?

A. So unstabilized polypropylene would be polypropylene without antioxidants. So using this as kind of a base case, because with antioxidants it depends a lot on what exactly is the antioxidants, so this unstabilized polypropylene is a really good sort of reference condition to think about.

Q. Okay. So if we talk about -- look at your chart and explain why this is significant to you and for the jury.

A. So I'd like to start with the black line first. So as I was saying earlier, this polypropylene degradation work in the '60s showed that it's happening at very high temperatures reacting with molecular oxygen, that we breath. So if you just take polypropylene, heat it up to 150 degrees C in the air, all the oxygen in the air can react with it.

When you think about the human body,

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it's at 37 degrees C. So it should be safe. You shouldn't have to worry about these reactions. And, in fact, you can estimate an induction time based on just thermal oxidation alone. So we're thinking about just the reaction of polypropylene with molecular oxygen catalyzed by heat, you can think in a way. You would expect an induction time of somewhere in the range of 20 years.

Q. Okay.

A. Think about a permanent implant, that's pretty good news.

Q. Okay. So let me see if I've got this right. Okay.

Thermal oxidation, is that predictive, is this 20-year period, in the human body?

A. Yes. That would be under what we would call physiological conditions, oxygen concentrations and temperatures that you would expect in the human body.

Q. Okay. But this is not in the human body?

A. This is predicted.

Q. Predicted.

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A. This is expected.
Q. Okay. Based upon what?
A. The work that was done in the 1960s, the -- characterizing the reaction.
Q. Okay. Was there anything that was later learned that proved that this product, when you put it in the body, isn't going to last 20 years?
MR. ANIELAK: Object to the characterization of "product."
THE COURT: The form of the question, the objection is sustained.
MR. MONSOUR: Let me rephrase. I'll re-ask my question, instead of saying "the product," I'll say "polypropylene." How's that?
BY MR. MONSOUR:
Q. Now you can answer the question.
A. So in these early experiments, so they implanted subcutaneously in a hamster, essentially just take a polypropylene suture, like a thin fiber, and you place it under the skin in a hamster. And they saw an induction time for unstabilized polypropylene of 100 days, approximately. So just imagine you did this

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experiment, this would be kind of a shocking finding.
And so at this time, the foreign body reaction, all of that wasn't really well-characterized and well-known. And so, you know, people speculated that there must be some enzymes -- there must be something in the body that's supplying oxygen that's much more reactive than the oxygen that we breathe. That was a major finding from this study. And, yes, so this is -- this is all for unstabilized polypropylene.
Q. Okay. So let me see if I understand this. This is unstabilized polypropylene, they anticipated that it would -- it was predicted to last 20 years, but when they actually put it into a living body, a hamster, they showed that instead of a 20-year useful life, it was closer for the induction phase of about 108 days, is that fair?
MR. ANIELAK: Leading.
A. That's right.
BY MR. MONSOUR:
Q. All right. Let me go to the next

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slide. And you're going to have to explain this one to me.
A. There's a lot here. So this study, and others that I was referring to, got people really thinking, well, what is it? What is it in the body that's causing this much faster oxidation? And so this, it's called essentially foreign body response or foreign body reaction. And it refers to what happens to a material when you implant it.
So what you're looking at here is just the biomaterial where you can see initially it's what we would call seated by monocytes, and monocytes are very small inflammatory cells. And then over a few days, those monocytes would differentiate or change to become macrophages, which can then fuse together, as shown in the bottom right corner. Fusion means you have a number of small cells that kind of combine together to form a large cell, a mini nuclei, to form these -- what's called foreign body giant cells.
And so the macrophages in the foreign body giant cells essentially seal off the

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biomaterial, creating what's called a privileged environment. So you have this pocket between the cell and the material surface where the cell is just secreting all these different things we call reactive oxygen species that are much more strong oxidizing agents than molecular oxygen.
Q. Okay. Real quick, real quick before you move on. The jury has already heard the word in this case "strong oxidizing agent" from a Phillips Sumika document. Could you explain to us; what is a strong oxidizing agent?
A. So a strong oxidizing agent would be something that has -- it's more potent than, say, molecular oxygen. It's more reactive, it's going to cause a faster reaction.
Q. Okay. Real quick, real quick; what's molecular oxygen?
A. Just oxygen in the air.
Q. That's what we're breathing?
A. Yeah.
Q. Okay. Keep going. Sorry.
A. So it's much more reactive. These can include things like peroxides, hypochlorous acid, hypochlorite, some things like you put in

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the swimming pool, these types of -- they have a very strong oxidizing, very reactive. And so -- and they also secrete acids and other things.

But all these chemicals are secreted into this privileged environment, they're sort of sealed off from the rest. So you have basically the material surface that's exposed to all these chemicals that are being secreted by the cells. That's what's meant in terms of the foreign body reaction.

Q. Okay. If I understand this from you, there's room oxygen, which is one level that can potentially degrade over whatever period of time, but in the body polypropylene would be exposed to a strong oxidizing agent which would lessen the time considerably?

MR. ANIELAK: Objection. Leading.

THE COURT: Sustained.

BY MR. MONSOUR:

Q. What do -- with regard to polypropylene in the body, what does a strong oxidizing agent do with regard to the longevity of polypropylene in the body?

A. Yes. So the -- what we know is if you

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have molecular oxygen reacting with polypropylene at high temperatures, it becomes important. So one way to think of this is it has something that's approaching that kind of reactivity. In other words, it's much stronger than that just reaction with molecular oxygen. The cells can make this a much more potent reactive oxygen from molecular oxygen, and that's what's causing this much more reactive species to be formed. It's going to react with the -- it's going to serve as a strong oxidizing agent that will react with the polypropylene.

Q. Okay. I want you to walk the jury through what happens to polypropylene once it's inside the body utilizing this slide. Go ahead.

A. So we start with this process of oxidation that I was just explaining in the previous slide, in this privileged space between these inflammatory cells. And the biomaterial, the polypropylene, is exposed to this very potent reactive oxygen species, that results in oxidation of the polypropylene. That then leads to this, what we call embrittlement. So when it gets sufficiently oxidized, which is a very,

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very -- this is all happening at the surface, so you don't need a very high degree of reaction before the polypropylene starts to become brittle. So it becomes brittle, it becomes hard. That means, if you follow the arrow going up, it loses its flexibility and ductility. So it's no longer flexible and stretchy, now it starts to become something like a hard plastic that can crack.

MR. MONSOUR: Your Honor, we've got a hand in the jury.

JUROR: I can't see the bottom line on the chart because there's two big notebooks on the table there.

THE COURT: Does that help, sir?

JUROR: Thank you.

BY MR. MONSOUR:

Q. All right.

A. So as it becomes embrittled, then it can crack, it's hard, no longer a ductile plastic.

Now, once this starts to crack, you can -- a number of things can happen. Mechanical breakage, so you can have pieces

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breaking off, sluffing off, causing problems. And also cracks result in the surface, so now there's more surface area exposed -- remember this is a surface area effect, and so now there's more surface exposed to cells, so this reaction is just going to continue. It's not going to continue until the device is removed, until the material is destroyed or extruded or pushed out of the body, but this process is going to continue as long as the material is there.

That's what we know about the foreign body reaction. And that's how it can lead to changes in mechanical properties that essentially you now have a material that's different from what you thought you implanted. It's changing over time.

Q. So we take polypropylene, put it into a mesh and implant it into a woman's vagina, will it suffer these failures?

A. So what we know about the -- this foreign body reaction will happen. We know the foreign body reaction will happen regardless of anything that you implant. Cells colonize the

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surface. What we know about polypropylene is that it responds to this reactive oxygen secreted by the cells. What we also know about polypropylene is that as it oxidizes, it becomes brittle. So we know that all these things are going to happen when the material is implanted.

What is unpredictable and unknown is when that will lead to a complication. My understanding in this case is that it did, but one of the challenges with using this, the problem of using this material in this space is that it is susceptible to oxidation, and the outcome of that process in terms of healing versus complications is very unpredictable and difficult to control. That would be --

Q. So why would it be problematic for a device like a polypropylene mesh when it's implanted in the vagina to become brittle, crack, and lose flexibility? Why would that be important?

MR. ANIELAK: Objection, your Honor. Beyond his expertise in terms of the clinical implications.

THE COURT: Just objection will

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suffice.

I'll see counsel for a moment, please.

(Sidebar.)

THE COURT: What was the objection? I couldn't --

MR. ANIELAK: Why would this be important to use in the vagina, he's not a medical doctor.

THE COURT: Well, he can answer.

MR. ANIELAK: My objection is this witness was asked a medical question. He's not a medical doctor, there's nothing in his disclosure concerning the medical application of polypropylene in terms of its vaginal use.

THE COURT: The witness may answer as to what is the significance of that fact.

MR. ANIELAK: He was asked the question asking for a medical opinion.

THE COURT: Right.

MR. MONSOUR: Let me re-ask it and talk about with regard to engineering and properties, if I ask that --

THE COURT: All right.

(End of sidebar.)

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BY MR. MONSOUR:

Q. Let me ask you this, Dr. Guelcher.

From an engineering standpoint, why could it be problematic for a mesh implant implanted in the vagina to lose flexibility, to become brittle and to crack? Why could that be important?

A. So my concern in this space is that you have very thin layers of soft tissue. So you've got a compliant plastic kind of between these layers of very thin soft tissue. And if that material now becomes brittle, the risk of an erosion or extrusion out of that soft tissue to me becomes very high, because there's just not much tissue separating it from a contaminated space essentially.

MR. ANIELAK: Objection, your Honor. Move to strike.

THE COURT: Sustained. The jurors will disregard the reference to separation from a contaminated space. The balance of the answer may stand.

MR. MONSOUR: Now, actually, hold on. Your Honor, I would like to offer into evidence

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three documents, which I believe have been pre-admitted, or pre-approved, I should say. I'm sorry.

THE COURT: Subject to prior rulings?

MR. MONSOUR: Subject to prior rulings by your Honor. The first one is entitled "TSM 308: Chemical Resistance of Marlex Polypropylene." And I would like to offer that as Exhibit Number 11.

THE CLERK: May it be marked, your Honor?

THE COURT: Yes, please.

(Whereupon, Exhibit Number 11, Document titled TSM 308: Chemical Resistance of Marlex Polypropylene, was marked in evidence.)

MR. MONSOUR: The second document I would like to offer into evidence, your Honor, is a Chevron Phillips Material Safety Data Sheet for Marlex polypropylene. This is the -- I believe it is the 2004, 2004 version. It has been pre-approved and redacted pursuant to your instructions.

THE COURT: All right.

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THE CLERK: Exhibit Number 12.
MR. MONSOUR: Exhibit Number 12.
(Whereupon, Exhibit Number 12, Chevron Phillips Material Safety Data Sheet for Marlex polypropylene, was marked in evidence.)
MR. MONSOUR: And, finally, a Marlex polypropylene data sheet from C.P. Chem Chevron Phillips Chemical from 1997, which was not originally on the approved sheet, but Mr. Anielak has agreed to at this point in time.
THE COURT: All right. That would be Exhibit 13.
MR. MONSOUR: Exhibit 13.
(Whereupon, Exhibit Number 13, C.P. Chem Chevron Phillips Chemical Marlex polypropylene data sheet from 1997, was marked in evidence.)
THE COURT: All right. Ladies and gentlemen, I may have told you earlier, and if I didn't I'll tell you now, certain of the documents that are admitted in evidence have been redacted in accordance with the rules of evidence. Again, that is a matter that's within

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my responsibility. You should not speculate about why material was removed. What you should focus on is what is in evidence, not what is not in evidence.
MR. ANIELAK: Your Honor, does Mr. Monsour have a copy for opposing counsel?
THE COURT: Do you have copies for counsel, please?
MR. MONSOUR: (Handing).
BY MR. MONSOUR:
Q. Now, if you would pull up --
The first document, Exhibit 11, is entitled "TSM 308: Chemical Resistance of Marlex Polypropylene."
Do you see that?
THE COURT: And ladies and gentlemen, just ignore the 14 in the bottom right-hand corner. The number -- the governing number is the number assigned in court, which is 11.
MR. MONSOUR: And to orient the jury, your Honor, thank you, the exhibit sticker for this document will appear in the upper right portion of the page when they get it.
BY MR. MONSOUR:

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Q. If you look to this document -- you are familiar with Marlex polypropylene, correct?
A. Yes. This is a document that discusses the chemical resistance.
MR. ANIELAK: Objection, your Honor.
THE COURT: Just if you would, if you could, you are familiar with the document, sir?
THE WITNESS: Yeah.
THE COURT: All right. Next question, please.
BY MR. MONSOUR:
Q. And is Marlex polypropylene a polypropylene that has antioxidants added to it?
MR. ANIELAK: Objection, your Honor.
THE COURT: This is beyond the scope of the issue we discussed this morning?
MR. ANIELAK: It is the same issue.
MR. MONSOUR: I can take this down and ask him a question.
THE COURT: May I see counsel?
(Sidebar.)
THE COURT: The battery is going, so if you can speak directly into the microphone.
MR. ANIELAK: The objection,

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your Honor, is there's nothing in his Rule 26 disclosure about this document. It was not on his reliance list, it was not provided in the deposition. I understand if he can read it --
MR. MONSOUR: Your Honor, this is basically the question all polypropylenes have antioxidants. I'm just going to say this is a polypropylene that had antioxidants, and I was going to move on. It's kind of like asking does a tree have bark on it. It's a basic --
THE COURT: The document is in evidence.
MR. MONSOUR: It is in evidence.
THE COURT: And you may ask him to read portions of the document.
May I see the document, please?
MR. MONSOUR: Sure.
THE COURT: I have some of them here, but I'm not sure --
MR. MONSOUR: Here's the actual exhibit with the exhibit sticker on it (handing).
THE COURT: All right. So you can ask if he prefers to read the title of the document,

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then you can ask him is there a Table 2, what is Table 2, and have him read what Table 2 is.
MR. MONSOUR: Okay. And then --
THE COURT: He can read from a document. You just have to frame your questions in terms of what does the document say.
MR. MONSOUR: Okay. I'll do that.
(End of sidebar.)
BY MR. MONSOUR:
Q. If you look at this document, Dr. Guelcher, and this is the document concerning the Marlex polypropylene, it says "Table 2 lists several strong mineral acids, halogens, and oxygen which can chemically attack Marlex polypropylene, causing degradation of the resin."
Do you see that?
A. Yes.
Q. Okay. Now, if you would flip to the next page where it says "Table 2."
So the first part of the page refer to Table 2 listing several strong acids, halogens, and oxygens, which can chemically attack Marlex polypropylene causing degradation. This has a

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list, and let's look at this. It says, "Marlex polypropylene has good chemical resistance to most mineral acids and bases, but like other polyolefins, can be attacked by some strong mineral acids, halogens, and oxygen."
Did I read that correctly?
A. Yes.
Q. "The effect of strong oxidizing agents is an attack on the polymer chain resulting in eventual embrittlement of the resin."
Do you see that?
A. Yes.
Q. Now, when they're talking about strong oxidizing agents, are those the strong oxidizing agents that you were just talking about?
MR. ANIELAK: Your Honor, same objection.
THE COURT: I'll permit the witness to answer that question.
THE WITNESS: Yes, they are. They're reactive species that are stronger oxidizing agents than molecular oxygen, like I said earlier.
BY MR. MONSOUR:

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Q. And they're in the human body?
A. Yes.
Q. Okay. And then when it talks to attacking the polymer chain resulting in eventual embrittlement of the resin, is that what you just talked about?
A. Yes.
MR. ANIELAK: Objection, your Honor.
THE COURT: You are going beyond the scope of the disclosure.
MR. MONSOUR: Okay. All right.
BY MR. MONSOUR:
Q. Let's go to Exhibit Number 12. This is the Material Safety Data Sheet for Marlex, which the Obtryx Advantage was made from.
Do you see that?
A. Yes.
Q. And you've seen it before, correct?
A. Yes.
Q. If you turn to Section 10, which is on Page 6. The first question, let me ask you; what's an MSDS sheet?
A. So an MSDS is a very important document that tells you all the hazards

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associated with a chemical. So before we ever use one, we always look at this to tell us how to protect ourselves, how to use it properly.
Q. Okay.
A. It's very important.
Q. So Section 10 of the MSDS for the --
THE COURT: The ruling was that the witness may read from the document.
MR. MONSOUR: Yes. Okay.
BY MR. MONSOUR:
Q. Read for me this part right here, Section 10. What does that say?
A. "Stability and reactivity."
Q. Okay. And then underneath here, it mentions "Incapability with other materials." What is listed after "Incompatibility with other materials"?
A. It says, "It may react with oxygen, strong oxidizing agents, such as chlorates, nitrates, peroxides, etcetera."
MR. MONSOUR: If you will pull up Exhibit 13, which is this one.
BY MR. MONSOUR:
Q. This is the 1997 Marlex MSDS sheet.

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If you will turn to Section E, "Reactivity data." Under "Reactivity data" for the 1997 Marlex data sheet, it says, "Incompatibility (Materials to Avoid)."

Dr. Guelcher, would you read for me what it says after that?

A. It says "Oxidants."

Q. Would that include the oxidants inside the body?

A. Yes.

MR. MONSOUR: You can pull that down.

BY MR. MONSOUR:

Q. Are the oxidants which are listed in these forms the types of oxidants which can lead to embrittlement?

MR. ANIELAK: Objection, your Honor.

THE COURT: Sustained.

And I'll see counsel briefly.

(Sidebar.)

THE COURT: It's just that the Rule 26(b) disclosure, which I required to avoid issues of this type, is dated June 25th, and there's no reference to Marlex and anything on the Marlex MSDS. That's the issue.

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MR. MONSOUR: I understand. It talks about polypropylene, which is -- I'm done.

THE COURT: Okay.

(End of sidebar.)

MR. MONSOUR: Your Honor, at this point in time, I will pass the witness. Thank you.

THE COURT: Thank you.

MR. ANIELAK: Your Honor, may I approach? I have a notebook for him.

CROSS EXAMINATION

BY MR. ANIELAK:

Q. Sir, I have your deposition transcripts and your trial testimony and your report. You may need to refer to those (handing).

A. Okay.

Q. Good morning, Dr. Guelcher.

A. Good morning.

Q. We have not had the opportunity to meet before. My name is Eric Anielak.

Try to keep your voice up, I'll try to remind you about that. The ventilation sometimes makes it hard to hear.

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If you don't understand one of my questions, just let me know, and I'll try to rephrase it. Okay?

A. Okay.

Q. Let's start by talking about Ms. Cardenas, because you did mention her.

When you formed your opinions in this case, you -- and when you authored your report, you knew nothing about Ms. Cardenas specifically, right?

A. I don't recall exactly what -- I did have some testimony on her medical problems, but I don't remember exactly when I received that.

Q. At the time you formed your report, when you authored your opinions in this case, you didn't have her medical records, right?

A. The report was based primarily on oxidation of polypropylene, so it wasn't directed toward her medical records.

Q. You didn't have a copy of Ms. Cardenas's medical records when you authored your report, right?

A. I did not have a copy of the records, no.

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Q. You had not reviewed any deposition testimony from the treating doctors of Ms. Cardenas, right?

A. No.

Q. At the time that you formed your opinions in this case, you didn't know -- you did not know what her complications were or what her medical course was, right?

A. No.

Q. At the time that you wrote your report and formed your opinions in this case, you didn't know what medical device Ms. Cardenas had implanted, right, specifically?

A. I don't remember. No, I don't think so.

Q. In fact, if we look in your report, Ms. Cardenas isn't mentioned in there at all. It's specifically -- the only thing in there is really a general discussion of polypropylene in terms of Ms. Cardenas, right?

A. That's what I addressed in the report, yeah.

Q. You talked about oxidation and degradation. And there are ways in which you

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can test for oxidation or degradation of polymers, right?
A. Yes.
Q. And Ms. Cardenas had her mesh actually explanted, right? Is that your understanding?
A. Yes.
Q. Okay. And you told the jury that the degradation process is unpredictable, it varies, in your opinion, from person to person, right?
A. No, that's not exactly what I said.
What I said is that there's a foreign body reaction, it will oxidize and respond and it will become brittle. What's unpredictable is the implications of that, the consequences, the complications. That's what I think I said.
Q. So each patient will have a unique -- their body will be unique in terms of ultimately how their body will respond to a medical implant at a cellular level, of course, right?
A. I don't know that I would say at a cellular level. I think that the foreign body reaction is going to happen when something is implanted. Whether or not it results in a complication is unpredictable, it depends on the

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timing, mechanical forces, other things like this that you can't control.
Q. There is a foreign body response that is expected, right?
A. It's known. I don't know that it works to the favor of this device, but it's -- I wouldn't use the word "expected." It's you know that it's going to happen, I guess.
Q. Okay. So you know that the body is going to respond to a medical device that's implanted, right?
A. Right.
Q. Okay. And what ultimately -- the specifics of how the body will respond to that device or potential complications, that would be unique from person to person, right? Because that's unpredictable?
A. Again, I just -- sorry, I just didn't like the way you said it.
I mean, we know that the foreign body reaction is going to happen, it's going to become brittle. What's unpredicted is the consequences of that observation. I would say it was more this way.

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Q. Okay. So how ultimately that device is going to function in an individual, it's unique to that person; fair enough?
A. It's unique to that person, but it needs to be considered in the design, it has to be taken into account. You have to have some way to mitigate that reaction.
Q. Sir, I'm just asking you; would you agree with me that how an individual responds to a medical device is unique to that person?
A. I just don't like -- I think I've responded. What I -- I mean, there are parts of that -- I think I responded more clearly exactly what I'm going to say. It's not necessarily -- there are aspects that are not just unique to one patient. What's unpredictable is the response, what happens after it becomes embrittled. But I don't like the phrasing, that when you implant a device it's going to be unique to the patient, I don't agree with all of that, I guess is what I'm saying.
Q. All right. Well, let's move on then.
Ms. Cardenas's sling was in place for approximately three years, is that right?

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A. It's my understanding.
Q. Okay. And you haven't performed any tests on her mesh that was removed, right?
A. We didn't have any explant material, so we couldn't test it.
Q. So you haven't tested any of the explant material from Ms. Cardenas, right?
A. We didn't, yes. We didn't have it.
Q. In fact, you've never tested any Boston Scientific mesh medical device for embrittlement, right? You've never done that?
A. So Dr. Dunn has done some of this work, but I've not done it.
Q. I'm asking about you.
And you have never tested a Boston Scientific device for embrittlement, right?
A. No.
Q. You've never taken a new medical device from Boston Scientific, a new mesh, and done any testing on a new piece of mesh from Boston Scientific, right?
A. Not in my tests. Dr. Dunn did that work.
Q. Sir, sir --

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MR. ANIELAK: And, your Honor, I'm asking Dr. Guelcher about his opinions and not other experts who are not here.

THE COURT: I think you need to define "you."

THE WITNESS: I'm sorry.

THE COURT: If you would wait for a question, sir.

THE WITNESS: Yes.

BY MR. ANIELAK:

Q. Sir, when I'm asking about what you've done, I'm asking about you personally, okay?

A. Okay. I'd just like to clarify that I work for Dr. Dunn's company, Polymer Chemical Technologies. And Dr. Dunn did the testing.

Q. Sir, that wasn't my question. My question was --

THE COURT: If you could, Dr. Guelcher, just listen to the question that's asked.

And when you ask a question that refers to "you," please define whether "you" means Dr. Guelcher personally or an entity with which he works.

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MR. MONSOUR: And I would just ask him to be allowed to complete his answers. He's --

THE COURT: No, because I have sustained the objection, so he may not.

THE WITNESS: Okay.

THE COURT: Put another question to the witness.

MR. ANIELAK: Thank you.

BY MR. ANIELAK:

Q. You personally haven't done testing on Boston Scientific's devices; true?

A. I have not personally tested.

Q. You personally have not tested devices manufactured by Boston Scientific that have been explanted; true?

A. I have not personally tested it.

Q. You mentioned Dr. Dunn a few times. I want to talk a little bit about him. You also talked about a company called Polymer Chemical Technologies.

You essentially have been hired by Dr. Dunn, is that right?

A. That's right.

Q. And Dr. Dunn owns a company called

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Polymer Chemical Technologies, is that right?

A. He does, yes.

Q. And he's the only employee of that company, is that right?

A. Yes, to my knowledge. He has -- well...

Q. And Dr. Dunn has been hired by the Plaintiff's lawyers?

A. That's right.

Q. Working for Plaintiff's lawyers in a variety of cases across the United States, right?

A. Yes.

Q. And Dr. Dunn recruited you to become involved in working for the Plaintiff's counsel as well, is that right?

A. Yes. Dr. Dunn wanted somebody that had some experience with biomaterials, so he talked to me about working with him on this litigation.

Q. And Dr. Dunn got you involved in about 2013, is that right?

A. I think, yes.

Q. And so in terms of how you're being

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paid, Dr. Dunn is paying for your time, is that right?

A. Technically I work for Dr. Dunn, yeah.

Q. And then Dr. Dunn is then charging the Plaintiff's counsel for the time that you're here. Is that how that works?

A. That's right.

Q. And so you personally are being paid -- is it $200 an hour to appear?

A. I think it's 210 now, I think.

Q. And is that an increase from the last month?

A. Yeah. Yes.

Q. And then Dr. Dunn then takes your fee and charges more to the Plaintiff's counsel for your time, is that right?

A. That's right. That's his business, yeah.

Q. And he charges approximately $350 an hour for your time to the Plaintiff's counsel, is that right?

A. No, no, no. It's not that much. There's a different rate for testifying versus non-testifying. It's something like 15 percent,

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because he has costs associated with running his business.

Q. And not only are you working with the Plaintiff's counsel in litigation against Boston Scientific, but you're also working with Plaintiff counsel in litigation involving other manufacturers of pelvic floor mesh devices, is that right?

A. That's right.

Q. And, in fact, the opinions that you've given here today regarding polypropylene, you've given against other manufacturers of polypropylene devices, is that right?

A. Yes.

Q. In fact, your opinions that you offer in this case and in other litigation involving other manufacturers, they essentially relate to polypropylene use in general, right, in the vaginal space?

A. They result -- they relate specifically to what I talked about today, how the body responds to -- this foreign body reaction and how polypropylene responds to that, yeah.

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Q. There are a number of different products in slings to treat stress urinary incontinence, a whole host of those. Your opinions relate to all of those polypropylene devices, right?

A. My opinions relate to polypropylene in general, I think.

Q. Now, I want to talk a little bit about the time before you got involved with the Plaintiff's lawyers in the litigation.

Prior to becoming involved in litigation, you had never studied polypropylene as an implantable biomaterial before; true?

A. Not as an implantable biomaterial. I was familiar with polypropylene.

Q. But as an implantable biomaterial, you had never studied polypropylene for that use prior to getting involved in the litigation; true?

A. That's true.

Q. And you talked to the jury about the degradation of polypropylene. Prior to your involvement with the Plaintiff's lawyers, you didn't conduct any research on polypropylene

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degradation, correct?

A. Well, as I explained, I work a lot with cell degradable polymers, cell response to biomaterials. And this was an interesting problem to me, because it looked like there was something going on with these devices, so I became interested in it. But I hadn't done work on it prior to that. That's what it's like to be a professor, I think.

Q. And, frankly, the research that you have done outside the litigation has not been involved with polypropylene, right? It has not involved polypropylene, your research?

A. No, but it relates to general principles that certainly apply to polypropylene.

Q. If you turn to the tab 3 of the notebook I've provided to you.

And you gave a deposition, that's right, in a different case, is that right?

A. This is for AMS.

Q. That's right.

A. This is probably the first one, I think.

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Q. And you took an oath at that time to tell the truth, is that right?

A. Yeah.

Q. And Page 20, I'm at line 22. Do you see that, behind tab 3?

A. Okay.

Q. And the question was, "Have you ever presented" -- I'm sorry. "Have you ever presented on polypropylene and its use as a surgical mesh?"

Do you see that question?

A. Yes.

Q. And your answer was, "Again, I have not. My research is not focused on polypropylene, so I have not presented on it."

Is that your answer?

A. Yes.

Q. Prior to the litigation, you'd never published any article on the body's response to polypropylene, right?

A. No.

Q. Prior to --

THE COURT: I'm sorry, when you say "no," are you saying no, that's not correct, or

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yes, it is correct? The question was you've never published on that --

THE WITNESS: I've never published on polypropylene, correct.

BY MR. ANIELAK:

Q. You've never published an article on polypropylene; that's true?

A. That's correct.

Q. It's also true that prior to the litigation you were not actively researching in the area of polypropylene mesh, right? That's true?

A. That's true.

Q. And it's also true that prior to the litigation, you never published any article on the use of polypropylene in mesh products, right?

A. Yes.

Q. In fact, I think you said this, you've never published on polypropylene at any time, right?

A. That's right.

Q. And you also mentioned to the -- in response to Mr. Monsour's questions about going

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to meetings and attending -- making presentations to your colleagues. Have you ever presented at one of those meetings on the topic of polypropylene?

A. No.

THE COURT: I think that's been asked and answered.

BY MR. ANIELAK:

Q. And you've never designed a polypropylene medical implant. That's true, too, right?

A. That's true.

Q. You went through some of your background with Mr. Monsour, and the places that you've been with industry.

And when you were working in industry, you were working in the field of biomaterials, is that right?

A. Industry was more conventional materials.

Q. Okay. And then you went to have an academic appointment at Vanderbilt in the area of biomaterials, right?

A. Yes. That's right.

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Q. And you went through the grants that you have received in the area of biomaterials and polymers, right?

A. Yes.

Q. And you've taught students about biomaterials and polymers, is that right?

A. Yes.

Q. In fact, I think you testified that you spent a lot of time studying the foreign body reaction to polymers, right?

A. Yes.

Q. And you outlined all of that experience for the jury, right?

A. Yes.

Q. And all of that experience was before you were ever involved in litigation, is that right?

A. Yes.

Q. And during all that time, before you were involved with the litigation, and all of that experience, you had not seen in any of your research that there was a problem with polypropylene mesh, right?

A. I don't believe so.

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Q. What I said was true?

A. Yes.

Q. I now want to talk about the foreign body response and make sure I understand the testimony that you're giving to the jury. And I think this was the fourth and fifth opinion related to foreign body response, is that right?

A. Seems reasonable.

Q. Okay. It's your opinion that when a medical device or a foreign material is put inside the body, it elicits an inflammatory response, correct?

A. Yes.

Q. And for mesh that's used to treat stress urinary incontinence, the mesh is designed to actually solicit a foreign body response? Tissue ingrowth is what the device's purpose is, correct? You understand that?

A. That's part of the -- I didn't talk about that, but that's part of the foreign body reaction is scar tissue, collagen deposition. That's part of it.

Q. You appreciate that the reason that it's a mesh is to allow tissue ingrowth into the

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pores, correct?
A. It's very similar to the scaffolds we design, you want tissue to grow into it, that's right.
Q. Right.
And the inflammatory response that you described, the cascade of inflammatory response, that occurs with, in your opinion, with the polypropylene mesh, right?
A. Yes. That's right.
Q. That foreign body response occurs with all medical devices that are permanently implanted; true?
A. Yes, that's what I was explaining.
Q. So what you described in terms of those pictures, that's not unique to polypropylene devices, right?
A. No. What's -- the foreign body reaction happens with any implanted material. What's unique is how the material responds to that. That's what I was saying.
Q. Right.
But all medical devices will cause the body to respond that are implanted, right?

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A. Yes.
Q. And the reactive oxygen species that you described, that would happen with polypropylene wherever it was placed in the body? That's not unique to a device treated for stress urinary incontinence, right?
A. Foreign body reaction will happen wherever it's implanted. What can vary is the consequences of that reaction. That's what I was saying.
Q. Very good.
But in terms of that reaction, the pictures that you showed, that would happen with polypropylene wherever polypropylene was placed in the body, right?
A. Yes.
Q. And notwithstanding the body's response to polypropylene and the reactive oxygenated species that you discussed, polypropylene has been used for decades in medical devices that have been permanently implanted in the body, right?
A. It has. But I don't believe you can extrapolate that to the specific conditions in

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the pelvic floor.
Q. Sir, my question was only limited to polypropylene that's been used for decades in medical devices in the body. Right?
A. It has. But -- sorry.
Q. And you actually agree that polypropylene can be a good material choice in medical applications, right?
A. So polypropylene has a favorable history in things like sutures. I'm not disputing that. What I'm saying is you cannot necessarily extrapolate what happens in one application to another without studying it in an appropriate preclinical model or preclinical trial. That's what I'm saying.
Q. Very good. And we're going to talk about that extrapolation. I'll put a mark by that and we'll come back to that.
The things like sutures, for example, those have been used for decades throughout the body made of polypropylene?
A. I'm not here to dispute the effectiveness of that. They have been used.
Q. And I'm not trying to dispute anything

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with you either. I'm just simply asking you if polypropylene sutures have been used for decades throughout the body.
A. They have been used.
Q. All right. And you've seen published literature that supports the use of polypropylene in a number of different medical applications, right?
A. Yes. And I've seen literature that doesn't.
Q. But there's certainly literature out there that supports the use of polypropylene in medical devices; fair?
A. Yes.
Q. And we can agree that polypropylene like, for example, sutures, have been used safely in the body for a number of years, decades, right?
A. I mean, I don't know the clinical literature. There are complications as far as the rates. I don't know. I just -- this isn't what I'm hear to talk about. But it has been used in the body, and still is used for things like sutures, I agree.

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Q. In fact, are you aware that polypropylene is used in things like surgical clips to close wounds? Are you aware of that?
A. Again, I don't know all the different uses of polypropylene in the body. I wasn't looking at that, but...
Q. Are you aware that polypropylene is used in heart surgery to repair septal defects or holes in the heart?
A. No.
Q. Are you aware that polypropylene is used to repair the outside of the heart when there needs to be a support to the outside tissue of the heart?
A. Not familiar with that.
Q. Are you familiar with polypropylene devices that are used in knee surgeries, in tendon repair?
A. No, I'm not that familiar with it. It is used in knees and things like this.
Q. Polypropylene is used as permanent devices in knees and shoulders and other joints. You're aware of that, right?
A. Yes.

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Q. And polypropylene is used in vascular applications and vascular grafts in the veins and the arteries. Are you aware of that as well?
A. No.
Q. Are you aware that polypropylene is used in the brain, in shunting, to create shunts when there is a fluid imbalance?
A. No.
Q. Are you aware that polypropylene has been used for hernia mesh? You're aware of that, right?
A. Yes, I'm aware of that.
Q. And hernia mesh has been used for many, many years, correct?
A. It has, but there are complications with that as well.
Q. There can be complications with any medical device, right, sir?
A. Yes, but --
Q. And polypropylene --
MR. MONSOUR: Objection. He was still talking.
THE COURT: Have you finished your

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answer, sir?
THE WITNESS: Well, I was just going to say that there's some evidence that those complications are related to the polypropylene mesh material and not just the surgery is what I was...
BY MR. ANIELAK:
Q. But there can be complications with any medical device, right?
A. It's very -- yes. It's a broad statement. Sure.
Q. And polypropylene mesh is used in abdominal surgery, in abdominal wall surgery, right?
A. Yes.
Q. And polypropylene mesh is used in gastrointestinal surgery. Are you aware of that as well?
A. No, not so much that one.
Q. You talked about your experience with devices for facial reconstruction?
A. That's right.
Q. Are you aware that polypropylene sutures are often used in facial and -- facial

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reconstruction, or rebuilding the jaw?
A. Sutures, yes. I mean --
Q. Are you aware --
A. -- I really don't use it actually because of -- well, I don't know what --
Q. Are you --
A. Use it for other materials, I'm sorry.
Q. That's all right.
Are you aware that polypropylene is used in eye surgery as well?
A. Not so familiar with that one.
Q. You talked about the area of the body in which the device was used was important. You made reference to that.
Are you aware that polypropylene sutures have been used to treat pelvic organ prolapse and stress urinary incontinence?
A. Again, it's a suture. It's not a mesh. It's a lot less material.
Q. Sir, that wasn't my question.
My only question was; are you aware that polypropylene sutures have been used to treat stress urinary incontinence in pelvic organ prolapse?

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A. Sutures are used everywhere in the body, yeah.
Q. And the polypropylene suture, do you know what the range of the diameter for the material comes in? Do you know how that's actually sold?
A. I know there's a range of diameters. I don't know exactly what they are, but, I mean...
Q. And are you also aware that the diameter of the actual fibers in the polypropylene mesh in the Obtryx device are consistent with the diameter of the polypropylene fibers used in sutures?
A. Yes, that's true.
Q. Dr. Blaivas discussed cutting sheets of polypropylene mesh and using it for various vaginal or urogynecologic applications. Are you aware that sheets of mesh have been around for 20 years for those kinds of applications?
A. Aware they've been around, not the details of what surgeons do with them.
Q. And generally you are -- you would agree that patients have been successfully

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treated with polypropylene slings, right? You agree with that generally?
MR. MONSOUR: Objection.
THE COURT: Sustained.
THE WITNESS: Yeah, I'm not really --
THE COURT: I sustained the objection, sir.
THE WITNESS: Okay. So I don't have to say -- okay. Thank you.
BY MR. ANIELAK:
Q. When Obtryx came on to the market in 2004, there had already been a history with the use of polypropylene in many of the devices that we just discussed, right?
A. Yes. Yeah.
Q. In fact, you agree with just the straightforward proposition that polypropylene, before Obtryx came on the market, was used throughout the body in a number of different applications, right?
A. That's true. It's been used a bit, quite a bit.
Q. And Boston Scientific considered the fact that polypropylene was used in many other

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medical devices when it decided to use polypropylene in its mesh. Are you aware of that?
MR. MONSOUR: Objection. Form.
THE COURT: Sustained. Sustained.
BY MR. ANIELAK:
Q. Is it appropriate -- strike that.
You would agree that it's appropriate for a company to look at historical use of materials when deciding on a future material to use? You agree generally that's the appropriate thing to do, right?
A. It's one factor to consider, but you have to consider other factors as well. It's not the only factor.
Q. All right. But it is a factor to consider when deciding on what material to use to look at what's been used and how it's been used before, right?
A. Yeah, it's a factor. We've done this before as well. It's commonly done.
Q. Historical performance of a material is one measure, it's one way to determine the suitability of a biomaterial for use in a

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medical device, right?
A. It's one measure, but it's not enough.
Q. But it is one measure. You agree with that?
A. It's a measure, yeah.
Q. You are a professor at Vanderbilt University, is that right?
A. That's right.
Q. You've been an associate professor there since 2012, is that right?
A. Right.
Q. And there is a medical school at Vanderbilt, is that right?
A. There is. We work with them.
Q. And you work with them?
A. Mm-hmm.
Q. And there's a whole range of different physicians at the medical school and hospital there, at Vanderbilt, is that right?
A. Yeah. They have all the major departments, hospital.
Q. And there are urologists there --
MR. MONSOUR: Objection.
THE COURT: Sustained.

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BY MR. ANIELAK:
Q. Doctor, have you --
THE COURT: I'm sustaining the objection.
MR. ANIELAK: I was going to reform --
THE COURT: I'll see counsel, please.
(Sidebar.)
THE COURT: Are you intending to ask him if --
MR. ANIELAK: If he warned any physicians at Vanderbilt University about any opinions he has. I think this is relevant.
MR. MONSOUR: It's going beyond --
THE COURT: I'm not going to permit that.
(End of sidebar.)
BY MR. ANIELAK:
Q. I want to talk about the Obtryx device in particular.
You haven't reviewed any studies involving Obtryx in particular, right?
A. No. Not for this report, no.
Q. And you don't know of any published reports of a degradation of the Obtryx device,

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right?
A. I mean, published reports of the polypropylene, but not this device.
Q. There are no published reports of the degradation of the Obtryx device, correct? True?
A. Not that I -- no.
Q. As far as you know, no doctor has ever reported that the Obtryx device has degraded, as far as you know, right?
A. I haven't seen it. I don't know. It's self-reporting, so...
Q. Well, at all the conferences that you've gone to, all of the literature that you have read, you haven't seen any physician reporting that the Obtryx device has degraded, right?
A. Yes.
Q. That's true?
A. That's true.
Q. You agree that potential degradation will be variable if it occurs in terms of any impact it might have on a woman, right?
A. I don't believe it's variable. I

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believe it's going to happen. I believe the timing and the consequences of that are unpredictable.
Q. Very good.
And the consequences of any oxidation or degradation you would say are highly variable and unpredictable, right?
A. They're unpredictable, yeah.
Q. You wouldn't say they're highly variable?
A. I suppose they're variable, too. I like unpredictable, because you can't design for it. As an engineer, I always worry about mitigating risks. And if I can't predict something, I can't design how to mitigate it. So that's...
Q. If you turn to your deposition behind tab 1, Page 48, line 4. Are you there?
A. Yeah. I see it says --
Q. Sir, let me just ask you the question.
So the question that was asked to you was, "Under your hypothesis, you're opining that oxidative degradation will occur 100 percent of the time when polypropylene is implanted in

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women?"
Do you see that?
A. Yes.
Q. And then your sworn answer was, "I think you have to be clear about what you mean by -- what I'm opining in the report is that inflammatory cells will release reactive oxygen species that can serve as a source of oxidative attack to polypropylene. Where that happens, when that happens, is very difficult to predict. It depends on a number of factors. But it will happen. How the device responds to that, again, is unpredictable. It's difficult to predict. But I'm basically saying that the process of reactive oxygen abstracting the proton and all that's described in the mechanism will happen in vivo, and the consequences will be highly variable and unpredictable."
Did I read that correctly?
A. You did. But I think I said I'm --
Q. Sir, my only question was; did I read that correctly?
MR. MONSOUR: Objection. Your Honor, he cut him off.

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THE COURT: Dr. Guelcher, just listen to the question that's asked, and then counsel will have an opportunity to ask you questions.
THE WITNESS: It's -- okay. I said highly variable and it is variable, but I said I prefer the word "predictable." Because it --
BY MR. ANIELAK:
Q. Just, sir --
THE COURT: Just -- no. If you would, put a question to the witness.
MR. ANIELAK: Thank you.
BY MR. ANIELAK:
Q. The bottom line is that you don't have data to correlate a specific complication to degradation of the polypropylene material, right? That's true?
A. I don't have those data, but I know it's going to oxidize, and I know it's going to get brittle and bad things can happen. I've not measured that.
Q. Sir, you don't have data to correlate a specific complication to degradation of the material, right?
A. No, I don't have the data, but --

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Q. Thank you.
In the case of Ms. Cardenas's treating physicians, Dr. Childs removed her mesh. Are you aware of that?
MR. MONSOUR: Objection.
THE COURT: Sustained.
MR. ANIELAK: I'm not sure I understand the objection.
THE COURT: I'll see counsel, please.
(Sidebar.)
THE COURT: Where are you going with this?
MR. ANIELAK: I'm going to ask him if Dr. Childs didn't note any embrittlement, or just the process happens all the time. I'm going to ask him about the specific facts. The doctor actually removed the mesh, he had the mesh in his hands.
THE COURT: But there's no -- I mean, do you have testimony that there was no embrittlement?
MR. ANIELAK: His report has nothing about embrittlement.
THE COURT: No.

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MR. ANIELAK: He doesn't report any embrittlement in the actual material.
THE COURT: You can ask him if he's reviewed a pathology report of the mesh that was explanted, and he can answer yes or no, and then you can offer evidence of what the pathology report showed.
MR. MONSOUR: He hasn't looked at any.
MR. ANIELAK: He hasn't addressed the embrittlement question.
THE COURT: You can establish that he hasn't looked at the report. You can't use him -- if he hasn't looked at the report and there's no other admissible evidence, you can't use him to prove that it wasn't embrittled.
Iakovlev is going to testify next, correct?
MR. ANIELAK: Yes.
MR. MONSOUR: Yes.
(End of sidebar.)
BY MR. ANIELAK:
Q. Sir, there was a pathology report that looked at the explanted material for Ms. Cardenas. Have you looked to that to see

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whether there was any description of embrittlement or any other characteristics of the mesh?
A. I have. I've seen it.
Q. The actual pathology report itself?
A. Oh, oh, I got confused. The pathology report?
Q. From the hospital.
A. Yeah, I don't remember that.
Q. You haven't seen -- you haven't looked at the pathology report from the hospital that looked at the actual mesh that was explanted from Ms. Cardenas, right?
A. I have not.
Q. You talked about and used the term "embrittlement" and "stiffness." And you said that embrittlement was one step before device failure, I think that's what your opinion was?
A. I said embrittlement can lead to device failure.
Q. Very good.
And whether or not embrittlement actually occurs in a patient, that's also unpredictable and variable, right?

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A. What's unpredictable is when it will happen.
Q. Very good.
When embrittlement will happen is unpredictable, right?
A. It will happen, but you just -- yeah.
Q. When embrittlement will happen is unpredictable, right?
A. When exactly, yeah. When it becomes embrittled, you don't know exactly when. You can't design for it, you can't control for it.
Q. You don't know of any mechanism by which embrittlement will translate into a complaint in a patient like pain or anything like that, right? You don't know of any mechanism like that; true?
A. I think having a brittle piece of plastic in soft tissue is going to hurt, but I'm not a medical doctor.
Q. If you turn to your deposition at Page 79.
THE COURT: Could I see counsel for a moment, please?
(Sidebar.)

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THE COURT: I just want to be clear here. You objected to counsel asking any questions of him with respect to clinical facts, correct?
MR. MONSOUR: Yes.
MR. ANIELAK: On Ms. Cardenas, correct.
THE COURT: On Mrs. Cardenas, and you're now opening it up, correct?
MR. ANIELAK: He hasn't looked at any of her medical records.
THE COURT: You're asking him questions about her.
MR. ANIELAK: Thank you, your Honor.
(End of sidebar.)
BY MR. ANIELAK:
Q. The first opinion that you offered dealt with inertness, is that right?
A. That's right.
Q. And you offered the opinion that polypropylene is not inert, is that right?
A. That's right.
Q. And under your definition of inertness, there's -- no material implant in the body will be inert, right?

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A. So biomaterials sciences don't like to use the word "inert," because when we think about biocompatibility, it really depends on where the material is, what it's being used for. So you can't say there's necessarily a biocompatible or inert material. It depends a lot on what you're trying to do with it. So that's why we don't like that word.
Q. Very good.
My only question was; any material that's implanted in the body, it will not be inert? There's no inert medical implant, right? It's not just -- let me start again. Let me start again.
Your opinion that polypropylene is not inert, it's not unique to polypropylene, any medical device implanted in the body will not be truly inert, right?
A. Nothing is truly inert, that's right, including polypropylene.
Q. I want to talk quickly about the ISO standards.
You agree that Boston Scientific

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completed the required ISO testing and evaluation of the Obtryx device for biocompatibility, right?
A. I did. ISO is required by FDA for devices. It's not the only thing you should do, but you have to do it. It's important.
Q. Right.
And Boston Scientific did that?
A. They did that.
MR. ANIELAK: Your Honor, I have an agreed upon exhibit that I'd like to mark.
What number are we up to?
MR. MONSOUR: What number is it on the agreed list?
MR. ANIELAK: 3589.
THE COURT: 14.
MR. ANIELAK: 14? I'd like to mark as Exhibit 14 the international standard, ISO-10993-1 as Exhibit 14.
(Whereupon, Exhibit Number 14, ISO-10993-1, was marked in evidence.)
MR. ANIELAK: May I approach the witness, your Honor?
THE COURT: Yes.

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MR. ANIELAK: (Handing.)
BY MR. ANIELAK:
Q. Sir, you are familiar with ISO-10993-1?
A. I've done a number of these tests in my own research.
Q. And this is an international --
MR. ANIELAK: Ms. Buso, can we make it a little bigger? Either my eyes are going bad or -- thank you.
BY MR. ANIELAK:
Q. This is the international standard for testing and evaluation of implantable materials?
A. It is.
Q. For biocompatibility, is that right?
A. That's right.
Q. And this evaluation and these standards are one way of determining whether or not a material for a medical device is suitable for implantation, is that right?
A. They're an important part of the regulatory process. You have to do them. But you don't just do them, you have to do other things as well. But you have to do this. It's

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required by regulatory bodies, yes.
Q. Okay. And these are the international standards, is that right?
A. Yes.
Q. And, essentially, the way that these standards are put together is that the International Standards Organization gets experts to form committees, and they meet to come to consensus about what testing should be done on biomaterials, is that right?
A. That's right.
Q. Essentially the folks that come together to develop these standards are specialists in the area, is that right?
A. That's right.
Q. And they're not just in the US, but they come from across the globe, is that right?
A. That's right.
Q. And like you said, these standards then guide companies in the development of biomaterials, right?
A. They do. But, again, it's not the only thing.
Q. I understand that.

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You've actually used these standards as a guide when you have looked at biomaterials; fair?
A. Some of our own biomaterials have passed these standards. But in our own more stringent studies, we've had problems and we had to go back and redesign. So this is my point.
Q. And I understand that's your point, but I just ask you to listen to my question.
MR. ANIELAK: And, your Honor, if he could just answer my question and be directed to do that, I'd appreciate it.
BY MR. ANIELAK:
Q. My question, sir, is, is you've actually utilized these particular standards in looking at biomaterials, right?
A. I've used some of them, yeah.
MR. ANIELAK: And if you to go Page 4 for me, Ms. Buso. I'm going to focus just maybe on the first paragraph. Ms. Buso, if you could blow up just that one so I could see it maybe a little bit better.
BY MR. ANIELAK:
Q. So this particular paragraph

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introduces this particular ISO standard, is that right?
A. Yes.
Q. And it describes the -- what we just talked about in terms of the third sentence down there, it says, "Each member body interested in the subject for which a technical committee has been established has the right to be represented on that committee."
Do you see that?
A. Yes.
Q. And there's also reference there to these particular standards being used by different regulatory organizations, right?
A. That's right.
MR. ANIELAK: And the -- Ms. Buso, if you could go down to the bottom for me, please, of the document, right there. That's great.
BY MR. ANIELAK:
Q. These particular standards then contain a number of different subparts that identify testing that can be done on different biomaterials, is that right?
A. Yeah. We've done some of these, yeah.

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Q. And, for example, there's a cytotoxicity test that you believe -- you've testified is a very stringent test, right?
A. Well, cytotoxicity is a stringent test for immediate toxicity. So you're essentially leaching things out over three days. So if there's something toxic that comes out in three days, you'll see it. So it's stringent from that perspective.
Q. There are other important tests that are listed on here, including mutagenicity testing, right?
A. Yes.
Q. And there's sensitization testing, allergic response testing, acute systemic testing. There's a whole battery of toxicity and biocompatibility testing that's in here, right?
A. Right.
Q. There are also -- in some cases, there are testing in animals that are discussed in these particular standards, is that right?
A. That's right.
Q. And you would agree that in some cases

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animal tests are an important way of assessing the suitability of a material for implantation, right?
A. Animal tests are critical. And it's also very important to use a test that's a good model for what you're trying to do in an animal before you put it in a human.
Q. Very good.
A. This is what we do.
MR. ANIELAK: And if you turn to Page 6 for me, Ms. Buso.
BY MR. ANIELAK:
Q. The ISO standard talks about animal testing, but the third paragraph there also -- I'm sorry, in the second paragraph, they also are trying to make the standard apply so it doesn't do unnecessary animal testing, right?
A. That is an important point.
Q. Very good.
But, ultimately, the third sentence summarizes what the purpose of the ISO standards are. And the purpose, as it states, is "The protection of humans is the primary goal of ISO 10993."

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That's what it says, right?
A. That's what it says, but it doesn't mean that if you do ISO, then it's safe. That's not what it's saying.
Q. Sir --
A. It's saying that's an intention.
Q. Sir, the ISO --
A. Yes.
Q. -- states that the protection of humans is the primary goal of ISO 10993. That's what it says, correct?
A. That's what it says, but -- I'm trying to follow the directions.
Q. Thank you.
I want to talk a little bit now about antioxidants.
Polypropylene is often stabilized using antioxidants, is that right?
A. Yes. In order to have any kind of useful service life, it needs antioxidants.
Q. Very good.
And when you talk about antioxidants, you agree that they make a difference in terms of preventing degradation, right?

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A. I wouldn't say they prevent it. I would say they inhibit or they slow its onset. So initially the antioxidants will react, but once they're depleted and consumed, there's nothing left to protect it from the oxidation process. They're delaying it. They're not necessarily preventing it or making it never happen. They're just delaying it.
Q. Fair enough.
The antioxidants actually delay, then, the oxidation process that may happen with a polymer like polypropylene, right?
A. That's what they're designed to do, yeah.
Q. And polypropylene that's used in medical applications often have antioxidants in them, is that right?
A. Yeah. My understanding is they're buying resins from suppliers that are used in other types of commercial application. But those oxidation packages are proprietary, they don't really disclose those.
Q. Okay. And you're aware that there are -- antioxidants are often in polypropylene

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that are used in medical applications, right?
A. Yeah, there are antioxidants packages in commercial polypropylene.
Q. You talk about extrapolation, and I wanted to go back and talk about extrapolation, and specifically with regard to this particular slide. This -- just so the jury is clear, this is a depiction of unstabilized polypropylene, is that right?
A. I think I made it clear when I was presenting this.
Q. You did. Right. I'm not accusing you that you didn't.
A. I'm not trying to hide. I said it was unstabilized.
Q. And unstabilized means it doesn't have antioxidants in it, correct?
A. That's right.
Q. All right. And so what you are showing here in terms of the time period, these were tests done with polypropylene without any antioxidants in them. That was what the authors said of the studies; true?
A. That's right.

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Q. And these -- part of these studies were done with polypropylene sheets without antioxidants that were put into ovens, is that right? Part of this analysis that you presented?
A. Okay. So the predicted line came from --
Can I give a --
THE COURT: Yes.
THE WITNESS: I can give a detailed answer to this?
THE COURT: You're not required to answer yes or no.
THE WITNESS: Yeah. Because -- okay. So what exactly was done is these experiments were done at high temperatures, at 150 degrees. And at those conditions, you can estimate what's called these rate constants. So you can calculate how fast the rate's going. And you can calculate what the rate would be at 37 degrees.
So they did the experiment at 150 degrees and 20 percent oxygen. And then they calculated the rate based on those

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experiments based on the rate log that you come up with. You can calculate the rate at which it will go away at 3 percent oxygen, which is the body, and 37 degrees C. That's where that number came from. But it didn't come from just putting it in an oven. It's more complicated than that.
BY MR. ANIELAK:
Q. It is. And I understand that.
But part of the data that you're relying upon for this chart was generated by putting polypropylene sheets without antioxidants into ovens, is that right?
A. Yeah. But I think I explained that that's one form, that's one way to oxidize it is thermally, but you can do it chemically as well.
Q. I understand that.
But you're extrapolating data from studies that were conducted in ovens?
A. It's not extrapolating. It's modelling.
And I teach a course on this called chemical reaction engineering. You do an experiment in the small reactor, you calculate

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rate log parameters, and then you -- I'll settle down.
So you -- it's a model. It's not an extrapolation, it's a model. And we teach on this, it's part of a course I've been teaching at Vanderbilt for eight years. And you model it in a small -- in one condition, and then you, in your design, you use that model for your design. So this is done all the time, it's not extrapolation.
Q. All right. Well, I'll use your term then.
You have modelled this chart based on testing of polypropylene sheets without antioxidants in ovens. You've used that data to model onto this chart, is that right?
A. We use those data to model the thermal oxidation process that would happen in the body --
Q. Very good.
A. -- based on other experiments. But it's a well-established, well-known approach that's been done for a long time.
Q. I'm just clarifying.

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A. I just -- if you drop the "ovens" term, I'd --
Q. Well, sir, when the study that you base this on was done, they heated it up in ovens, right?
A. I know, you're making some certain connotation. What I'm trying to say is, there's a sound rationale for doing this. I do this in my course.
Q. I'm just simply asking you if part --
THE COURT: I think you've exhausted the topic.
BY MR. ANIELAK:
Q. You also talked about less mesh being better. That was one of the opinions that you offered?
A. That's right.
Q. And one of the pieces of material we have in evidence is the Obtryx sling.
THE COURT: I think it's marked for identification. I don't know that it's been marked as an exhibit yet.
MR. ANIELAK: It is.
MS. MURPHY: I don't think it has,

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your Honor. I think it's C for identification.
THE COURT: Are both sides offering it?
MR. ANIELAK: We'll offer it. We can offer it.
THE COURT: All right. It should be marked as an exhibit, please. That would be 15?
THE CLERK: Yes, your Honor.
THE COURT: Thank you.
(Whereupon, Exhibit Number 15, Obtryx sling, was marked in evidence.)
BY MR. ANIELAK:
Q. Sir, I've marked as Exhibit Number 15 --
MR. ANIELAK: May I approach, your Honor?
THE COURT: Yes.
BY MR. ANIELAK:
Q. A copy of the -- a copy -- the Obtryx sling. Have you ever held that Obtryx sling before?
A. I believe so. We had some -- Dr. Dunn's company had some samples.
Q. You're not offering any opinion that

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there are slings that are of a different size in terms of its footprint than the Obtryx sling, are you?
A. No. I'm offering the opinion that less mesh is better, which you extrapolate that, then no mesh is better eventually. But, I mean, less mesh means less foreign body reaction, is what I'm saying.
Q. My only question is; you're not offering an opinion that there are other slings, polypropylene slings out there that have a smaller footprint? You're not offering that opinion?
A. I'm not really speaking to that today.
MR. ANIELAK: Thank you.
I think that's all the questions I have, your Honor.
THE COURT: Do any of the jurors have questions for the witness? No?
All right. Then we'll take the morning recess for 15 minutes, and we'll resume at 11:15, or as soon after that as the jurors are ready. The jurors are excused.
THE COURT OFFICER: All rise. Jury

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out.
THE COURT: Oh, I'm sorry, did you have any redirect?
MR. MONSOUR: Yes, we do, your Honor.
THE COURT: We'll still take the morning recess. I did skip a step there, I'm sorry.
(Jury not present.)
MR. OSBORNE: Your Honor, during the break can we get the microscope set up for the next witness so we don't have to stop and do that? I don't want it to be a distraction.
THE COURT: How large is it?
MR. OSBORNE: It's about this big (indicating).
THE COURT: Okay.
MR. MONSOUR: My redirect is going to be short, so we'll --
THE COURT: All right. Yes, you may do that now.
MR. OSBORNE: Okay. Thank you.
THE CLERK: Court will stand in recess.
(Whereupon, a recess was taken from

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11:02 a.m. to 11:15 a.m.)
THE CLERK: Court. All rise, please.
THE COURT OFFICER: All rise. Jury in. Jury entering.
(Jury present.)
THE COURT OFFICER: Court is in session. You may be seated.
THE COURT: All right. Sir, you're still under oath.
THE WITNESS: Yes.
REDIRECT EXAMINATION
BY MR. MONSOUR:
Q. Dr. Guelcher, just a few follow-up questions. You were asked by Mr. Anielak about whether or not you'd ever looked at or tested any of the Obtryx materials.
Do you remember those questions?
A. Yes, that's right.
Q. You work with a gentleman -- what's his name?
MR. ANIELAK: Your Honor, may we approach?
THE COURT: Not at this time.
A. Dr. Russell Dunn.

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BY MR. MONSOUR:
Q. Okay. And explain to the jury how you and Dr. Dunn work together in looking at this type of information.
A. So Dr. Dunn is a professor of practice at Vanderbilt, so he focuses on courses that have a sort of professional practice element. He also owns a consulting business, and I've been subcontracting for him through that consulting business, so he pays me on an hourly rate, and it covers the cost of running that business, which is helpful for me because with all the grant writing and students and things, it's difficult. So it's his company, and I contract to him to talk about the biomaterials aspects.
Q. And do you all work together and use each other's information with regard to this consulting that you do on biomaterials and transvaginal mesh?
A. Yes --
MR. ANIELAK: Your Honor, may we approach?
THE COURT: Just a yes or no answer, please.
A. Yes.
BY MR. MONSOUR:
Q. Okay. Have you and Dr. Dunn ever had a chance to look at the oxidation of any Obtryx mesh?
MR. ANIELAK: Your Honor, may we approach?
THE COURT: Yes, now you may.
(Sidebar.)
MR. ANIELAK: Sorry. I was trying to head that off.
THE COURT: All right. No, I knew exactly what was happening, but he was entitled to ask certainly those questions.
MR. ANIELAK: Sure.
THE COURT: He has said that he did not personally, so what do you expect that you're going to ask him?
MR. MONSOUR: The reason that he didn't do it personally is Dr. Dunn is the one that does that, and then they share the results together.
THE COURT: All right. He can testify

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about what role Dr. Dunn plays and what role he plays, but not about Dunn's test results.
MR. MONSOUR: But it does me no good --
MR. ANIELAK: It's not in his designation, anything about Dr. Dunn's testimony.
THE COURT: Are you talking to each other?
MR. ANIELAK: I'm sorry.
There's nothing in his designation about Dr. Dunn's test results or relying on Dr. Dunn's testing. It's not there.
MR. MONSOUR: The point that I --
THE COURT: The problem is that you can't parlay the fact that something is beyond the scope, and you did with the clinical into freedom to ask anything you want about it, and then foreclose the other side from addressing it. That's the difficulty. So, basically, the extent to which you are permitted to go was to -- was the extent that you were permitted to go was to establish that he personally had not done that testing, so the

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Plaintiff is entitled to show that he did not personally do that testing, but that Dr. Dunn had done some testing, and he was familiar with the results, not what the results are.

MR. MONSOUR: Okay.

THE COURT: All right.

(End of sidebar.)

BY MR. MONSOUR:

Q. My question is very specific.

In working with Dr. Dunn, Dr. Dunn has looked at the oxidation of Obtryx, correct?

A. He has.

Q. Okay. So this is not something that your group has ignored; fair statement?

A. That's right.

Q. Okay. Now, you were asked by Mr. Anielak if you had ever looked at any clinical trials or published reports on the degradation of Obtryx.

Do you remember that question?

A. Yes.

Q. Are any such reports published?

A. I haven't seen them. Yeah, I don't know.

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Q. Okay. You had mentioned in response to some questions that polypropylene, along with other materials, none of them are inert, correct?

A. That's right.

Q. Are there levels of implants in the body, some products being more reactive in the body and others being less?

A. So with respect to specifically oxidation, I had the one slide that showed polypropylene being one of the more easily oxidized and another materials are less. So again, some materials -- how the materials respond to that foreign body reaction varies, so there are varying degrees of response.

Q. Okay. So could you explain to the jury, knowing that some materials are more reactive than others, why is selection of the appropriate material for a certain area of the body important? Why is that important?

A. So we see this in our own work. Grafts that we make for skin have to be designed very differently than those for the bone. You have to take into account the anatomic site, so

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it's very important to use preclinical models that model what you're trying to do in animals. So in a bone you would use a bone void filler, and in skin you would use an open wound in a pig. But it's very important to test these preclinical models for their intended purpose. That's the type of work that we do to evaluate the materials.

Q. You were also presented information about ISO testing.

Do you remember that?

A. Yeah.

Q. Okay. Just because a product passes ISO testing, does that mean it's good to go, good to implant, should we implant it in the body?

A. So I'm referring to personally.

So for bone void filler, the FDA requires a large animal defect. Four months, you have to look at four months and see if there's good healing. Our defects were healing well at four months, but because of the degradation problems, we thought we really needed to look at a year, and in a year we see

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problems, so we would have to go back and change it.

So the way I have always looked at the ISO standard is you have to do it. The FDA, Europe requires it. It's important. It tells you a lot. And its aim is to protect patients. That's the goal of the ISO standards. It's our responsibility in engineering and science. If I'm going to implant this in someone, I have to look at all the things that can happen, know what's going to happen, design to mitigate that risk if I can. That's just the way that we approach it.

So it takes time, it slows us down, it's disappointing, but we have to fix it before it can go into patients, and evaluate it in preclinical models. But ISO is just the beginning. I think a responsible scientist or engineer has to look and say I have got to be sure, I really have to know. That's my approach.

Q. Okay. Next question. You were asked about antioxidants, unstable versus -- or unstabilized polypropylene. So if we add an

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antioxidant to polypropylene, good to go forever in vaginal mesh?
A. There's just no way to test that. Antioxidants delay oxidation embrittlement, but they don't prevent it from ever happening. I mean, so it's just really difficult to guarantee that when it becomes minimal, it will become oxidizing embrittlement, what will that do, what will be the consequences of that? As I said, they're difficult to predict, and that's what concerns me about it. I would be much more comfortable with the more durable material that is more stable. And we see examples of this in the industry, people that are doing this.
Q. Such as?
A. Such as, you know, polyurethane catheters which degrade by oxidation, and those have been stabilized by antioxidants, but it's just not enough. So there's research being done to try to find more stable materials. And you can't have your pacemaker short out, this is disaster. So we need to really make sure that these things are going to last for a long time, and so that's the approach that I see a lot is

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if you have an unstable material, let's do it better.
I just don't think you can rely on antioxidants. You don't even know how these antioxidants will respond in the body. They're designed for high temperatures. We just don't know what they'll do.
Q. And isn't it true that some antioxidants that bear -- that have some polypropylenes that have antioxidants, they still react with reactive oxidative species?
MR. ANIELAK: Objection, your Honor.
THE COURT: Sustained as to form. Leading.
MR. MONSOUR: I'm sorry.
BY MR. MONSOUR:
Q. Antioxidants that are added to polypropylene, will that prevent certain strong oxidizing agents from attacking that within the body?
A. It's not known. The oxidative species are different, and my knowledge how those antioxidants will protect an implant in the body is just really not known. I don't know that

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it's been studied. They're optimized for commercial use.
Q. Which means what?
A. Playground equipment, tree stands, or deer stands, just anything made out of polypropylene that's exposed to the environment, not in the body.
MR. MONSOUR: I'll pass the witness. Thank you.
MR. ANIELAK: No questions, your Honor.
THE COURT: All right. Now do any of the jurors have questions for the witness? No?
All right. Thank you, sir. You may step down.
THE WITNESS: Leave this?
THE COURT: Yes.
Is it your notebook that's on the witness stand?
MR. ANIELAK: It is.
THE COURT: Would you retrieve it, please?
MR. ANIELAK: Sure.
THE COURT: The next witness.

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MR. OSBORNE: Yes, your Honor.
The Plaintiff would call Dr. Vladimir Iakovlev.
THE COURT OFFICER: Stop right here, please. Face the clerk.

VLADIMIR V. IAKOVLEV, MD, having been duly sworn, was examined and testified as follows:
THE CLERK: Please be seated.
DIRECT EXAMINATION
BY MR. OSBORNE:
Q. Good morning.
A. Good morning.
Q. Tell us your name, please.
A. Vladimir Iakovlev.
Q. And, sir, what is your occupation?
A. I'm an anatomical pathologist.
Q. Tell us what an anatomical pathologist does.
A. An anatomical pathologist examines human tissue and renders diagnoses in the context of clinical presentation of the patients.

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Q. And where do you work?
A. I work at St. Michael's Hospital, and I hold appointment at University of Toronto department of laboratory medicine and pathobiology in Toronto, Canada.
Q. Where is St. Michael's Hospital located?
A. St. Michael's Hospital is in downtown Toronto, a Province of Ontario, Canada.
Q. And how long have you worked there?
A. I have worked there for seven years.
Q. And what is your current position?
A. Currently, I'm a doctor of cytopathology, division of pathology, and I am anatomical pathologist.
Q. And what are your duties and responsibilities as the director of cytopathology at St. Michael's?
A. As the director of cytopathology, I oversee work of cytotechnologists and cytopathologists, I conduct quality assurance programs in the division of cytopathology, and as an anatomical pathologist I render diagnoses, make diagnosis using tissue from patients. My

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current annual volume is about 4 to 5,000 cases a year.
Q. And briefly describe your education and training that prepares you to work as a pathologist.
A. I did my residency training in University of Manitoba. It was anatomical pathology residency accredited by both Royal College of Physicians of Canada and the American Board of Pathology.
After completion of anatomical pathology training, I went for two years of research training at Ontario Cancer Institute, Princess Margaret Hospital in Toronto.
And after I completed that training, I accepted positions at St. Michael's Hospital and worked there since.
Q. Do you currently have any teaching responsibilities?
A. Yes. As an academic pathologist, I teach medical students, graduate students, master's students. I teach residents and fellows, which is postgraduate education. And I teach course for physical therapists in

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continuing medical education course for physiotherapists.
Q. Tell us a little bit about your research interests.
A. My research interests started in -- during research training during my years of fellowship at Princess Margaret Hospital. My main focus at that time was three-dimensional or spatial distribution of biomarkers in human tissue. The main thing is moving, and the major focus of research, medical research is cancer research, and as you know, that cancer research is trying to convert approaches for treatment -- for medical treatment rather than surgical.
As we treat infections with antibiotics, we try to identify antibiotics which can kill specific bacteria, so we take samples of bacteria from patients, and then we test for sensitivity for antibiotics.
The same way is going to happen with some cancer treatment. A small biopsy will be taken from cancer or from tumor from a patient, it will be analyzed, then a set of drugs will be used to treat this cancer, based on this test,

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because we can identify sensitivity for specific drugs.
However, the problem is that tumors are not uniform. There might be several parts of the tumor which can be responsive to one drug or to another drug. And I was working on the methodology, how you sample the tumors so you can have accurate results for sensitivity of these drugs.
Q. All right. And where do you hold medical licenses?
A. I hold a medical license in Province of Ontario, Canada, and State of Michigan, United States. And I'm certified to practice anatomical pathology by Royal College of Pathologists, or Physicians of Canada, and the American Board of Pathology. I'm also a fellow of the American College of Pathologists.
Q. And have you written articles that have been published in the scientific literature?
A. Currently, I have about 20 full-size peer-reviewed articles, over 30 abstracts, and some presentations.

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Q. All right. And in your practice as an anatomical pathologist, have you developed an interest in the evaluation of surgical meshes?

A. My interest in surgical meshes started in 2012. As I mentioned, I had interest in three-dimensional distribution or spatial distribution within human tissue. And Robert Bendavid, Dr. Robert Bendavid, he's a recognized authority in hernia repair, approached me with this offer to do collaborative project on explanted hernia meshes. That's how it all started.

And I suddenly realized when I was reviewing published literature that there was not much in terms of pathology published on these meshes. Pathologists are too busy. They are working on cancer cases, and if it's not malignant, you just don't pay much attention. I was appalled that half of the specimens don't even get microscopy examination. The surgical meshes are just being discarded. I mean, there's no microscopy. And I saw there was a gap in knowledge and was -- started exploring the area.

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Q. And through your work with Dr. Bendavid, have you actually looked and analyzed surgical meshes?

A. Yes. He submitted initial set of samples of hernia meshes, which explanted, or taken out, because explantation is the process when the implant is taken out. Implantation when the object is placed in the body; explantation is when it's taken out.

So he submitted explanted hernia meshes to me, and I also researched what was submitted to St. Michael's Hospital at the time, and that's how my pool of samples started building up.

Q. Has that pool of samples also included transvaginal meshes that have been removed?

A. Yes. Total right now, my pool of samples contains about 130 samples of explanted meshes. This include anterior abdominal wall, inguinal hernia meshes, transvaginal meshes. They come from different sources from St. Michael's patients, from Shouldice Hospital patients, and from some of the potential litigation cases. The meshes are at least four

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different manufacturers, and maybe six or seven, maybe even more different models of meshes.

Q. Have you examined samples of Boston Scientific's sling mesh?

A. Yes. This pool includes a number of Boston Scientific sling meshes.

Q. All right. Now, based on your work and training, did we ask you to be an expert in this case?

A. Yes.

Q. And do you charge for your time here in court today?

A. Yes, I do.

Q. And have you charged for your time to prepare to come to testify in court?

A. Yes, I do.

Q. What are your charges?

A. I charge $400 an hour. And I charge only for the work I do to prepare the reports. I don't charge for literature search or -- I consider this as part of my research interest.

Q. And were you provided materials by me to review specific to Maria Cardenas?

A. Yes. Initially I received clinical

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records of the patient, and then later on I received slides of the specimen taken out of Maria Cardenas.

Q. Okay. Let's review some of that.

Did you review the medical records of Dr. Childs?

A. Yes, I did.

Q. Did you review the medical records of Alta View Hospital?

A. Yes, I did.

Q. Did you review the medical records of Dr. Anders?

A. Yes, I did.

Q. Did you review the medical records of Riverton Hospital?

A. Yes, yes, it was there.

Q. And did you review the records of Dr. Stout?

A. Yes.

Q. And then, as you indicated, I think sometime after reviewing the records you also received some pathology slides of Mrs. Cardenas, is that right?

A. Yes, later on I received slides of the

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specimen.
Q. Did you also have a chance to review the pathology report of Dr. Campana from the January, 2011 removal surgery that was done on Mrs. Cardenas?
A. Yes, the slides were accompanied by the pathology report.
MR. OSBORNE: Would you go ahead and pull up the pathology slide for me?
THE COURT: Doctor, you might be more comfortable if you pull the microphone closer to you, then you won't have to lean forward so much.
THE WITNESS: Thank you.
BY MR. OSBORNE:
Q. I think if you look up on the board, it's a little bit far away, Dr. Iakovlev, but does that appear to be the pathology report from the analysis Dr. Campana did in the pathology department at Alta View Hospital?
A. Yes, it looks like that report.
Q. Can you just briefly explain to the jury what the specimen consisted of that Dr. Campana evaluated?

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A. The specimen was described grossly. This is a typical pathology report. Pathologists receive the specimen, they describe the specimen, what they see grossly, and there is gross examination. Grossly means without microscope, just how we see. And the description was that there was a piece of mesh with some material tissue, and the size of it.
Then this specimen, if it's large, has been sectioned. If it's small, the whole specimen goes into processing machines. And after processing, the specimen is being imbedded into paraffin block or paraffin, a small piece of paraffin. Then this paraffin sits on a plastic cassette, and then it's loaded on a microfilm, and thin slice of the tissue like paraffin is made. It's like a slice of salami or ham. And then this thin slice is placed on glass slide, and then the tissue can be stained. Because without staining, it's transparent, you do not see much, but you can stain and then see features under the microscope.
So I received gross slides with thin slices of the specimen which I could stain. One

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of them was stained, and five of them were not stained, and I could do other stains.
Q. And just so it's clear, so the specimen that Dr. Campana evaluated, that contained tissue from Mrs. Cardenas, from her removal surgery, is that right?
A. Yes, for removal surgery in January, 2011.
Q. And the specimen that Dr. Campana evaluated also contained a piece of the mesh that was taken from her, is that correct?
A. Yes, mesh and tissue.
Q. And you've just described what I believe to be this recoup process where you could then get portions of that material for you to review as well, correct?
A. Yes.
Q. Okay. So just so it's clear, the slides you reviewed, that came from the same tissue sample Dr. Campana reviewed, correct?
A. Yes.
Q. All right. And the slides you reviewed actually contained pieces of tissue and of the mesh taken from Mrs. Cardenas, is that

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right?
MS. MURPHY: Objection, your Honor. Leading.
THE COURT: I'll permit it at this point.
A. Yes, they were labeled accordingly. Sizes and labelling was corresponding, and the patient's name was on the pathology report, yes.
BY MR. OSBORNE:
Q. Okay. Now, did you use a microscope to look at Mrs. Cardenas's tissue and the mesh?
A. Yes, that is my custom.
Q. And does the microscope allow you to take pictures of the slides?
A. Yes, you can see camera is on top.
THE COURT: I can't hear you, sir.
A. Yes, I can take pictures when the camera is loaded on the top of microscope, as you can see here.
BY MR. OSBORNE:
Q. Okay. And did you take pictures of Mrs. Cardenas's slides?
A. Yes, I did.
Q. And how many slides were you provided?

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A. As I mentioned, I received one stained slide, H&E. H&E is the typical basic stain for initial evaluation, hematoxylin I'm using, and then I received five unstained slides.

Q. I know you've touched upon it, but just give the jury a general description of what staining is and why it's important.

A. Tissue without staining is transparent because the thin slice is so thin that light shines through and you see just outlines, but you don't see the features. The stains, they stain tissue, and then it's visible under the microscope.

There are two types of staining. One is histochemical stain, which use approximately the same dyes as we use to stain fabric or dye fabric, and they stain different structures in tissue, and as I said, we can visualize it. Some stains stain proteins, some stains stain DNA or chromosomes. And then there is a more complicated, sophisticated way of staining when we use antibodies of animals, which is immunoglobulins which float in animal blood. But the animals have specific proteins

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introduced in their body, and their immune system develop antibodies against specific human protein. We can take out these antibodies, can apply them to the glass slide with tissue, they will attack this protein which was initially introduced to their body, and then the antibodies are labeled, and then we can see color of specific protein. So this staining would be more of a specific staining for specific proteins.

Q. What is polarization as it pertains to your analysis of the slides?

A. Polarization allows us to see objects which are transparent, because if it's transparent and it doesn't have color, on the light microscope you don't see it, it's a white background. But with polarization, other structures become dark, but the structure with optical properties suddenly becomes bright and we can see it.

Q. Now, before we move forward, let's discuss some medical terms from a pathology perspective that we're going to be looking at in terms of the slides in the pictures.

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First off, what is inflammation?

A. Inflammation is response of human body against noxious -- you know, against something which is bad for the body. It can be bacteria, or it can be foreign object, or it can be dead tissue which body needs to clear out, to remove, to cure bacteria and remove it, or to degrade, destroy foreign body and remove it, or dead tissue which needs to be also digested and removed. That's how inflammation keeps our body healthy.

Q. What is edema?

A. Edema is accumulation of fluid in the tissue. We probably all experienced it at will, or swelling is actually a result of edema when fluid collects in the area and the tissue expands, becomes large, this edema, swelling.

Q. What is a foreign body reaction?

A. Foreign body reaction is specific reaction of immune system against a foreign body. It usually is composed of macrophages, a small amount of lymphocytes.

The macrophages, when they cannot kill the foreign object and the foreign object is too

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large, they join together, they fuse together and become multinucleated. It's like a one cell which incorporates several cells. We call them multinucleated giant cells.

Q. And what is fibrosis?

A. Fibrosis is a nonspecific reaction of the body to repair. It's like a glue. If we have a wound or incision, we need to connect tissue back together, and the way the human body does it, it fills it up with nonspecific glue or fibrous tissue. Because human body has very limited ability to regenerate. We cannot regenerate our own limbs as lizards. So we use fibrous tissue, not specifically to fill gaps of damaged tissue. That tissue is held together by the scar. Fibrous tissue and scar are used interchangeably. Fibrosis scarring are interchangeable terms.

Q. Now, we're going to start looking at the pictures, but let me ask you a couple questions.

Were the photographs that the jury is about to see, were they taken by you?

A. Yes.

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Q. And were those photographs taken of Mrs. Cardenas's pathology slides?
A. Yes.
Q. And do the photographs fairly and accurately represent the slides you reviewed?
A. Yes.
MR. OSBORNE: Your Honor, at this time, I'd like to see if I could bring the easel over and put the photographs up for the jury.
THE COURT: Yes. First, if you would just mark the boards for identification.
MR. OSBORNE: Sure.
THE COURT: And then when you put them up and the witness testifies, refer to it by letter for the record.
MR. OSBORNE: Sure, Judge.
We have five photographs.
(Whereupon, Exhibits I, Blow-up photograph of Figure 1A, J, Blow-up photograph of Figure 2, K, Blow-up photograph of Figure 7B, L, Blow-up photograph of Figure 7C, M, Blow-up photograph of Figure 8, were marked for identification.)

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BY MR. OSBORNE:
Q. Dr. Iakovlev, is this photograph or Figure 1A from one of the pictures that you took of Mrs. Cardenas's slides?
A. Yes.
Q. Okay. I'm going to go ahead and put it up on the easel. And would it help you to come down be able to point to the photograph in order to explain the findings?
A. Yes, it would be easier for me to be there.
THE COURT: All right. You may, sir, but you must face the jurors when you speak, and please keep your voice up so the court reporter and I can hear you. Yes, thank you.
A. The photographs are arranged that there are two copies of the same image. One copy is unaltered image, and the other copy has some labelling, and also the spaces where mesh filaments are filled with yellow color.
THE COURT: I'm not able to hear the end of what you just said, sir. The same image.
A. Right copy of the image has labelling and clear spaces which are from mesh filaments

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are filled yellow color.
BY MR. OSBORNE:
Q. Dr. Iakovlev, I suggest that you stand on this side, and the Judge and the jury can both hear you.
A. Because the mesh is composed of filaments. When the microtome knife cuts through them, we see cross-sections the same as salami, because salami is more like a filament. When you take a cross-section, it's like a pancake. So this would be a pancake. Because polypropylene is clear, it's white space. Also polypropylene doesn't adhere to glass slide well. Most of the --
THE COURT: Sorry. It's too difficult for the court reporter and for me to hear.
BY MR. OSBORNE:
Q. You've got to keep your voice up. Maybe we can move it over a little bit so it's a little bit closer.
THE COURT: Are the jurors -- I should ask. I can't see the jurors. Have the jurors been able to hear? If you can't at any time, please speak up.

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A. So I was explaining that filaments which are composing mesh can be compared with salami, and when the knife of microtome cuts it, it makes thin slices, and these thin slices when they're on the glass slide, they're clear because polypropylene is clear material, or because it adheres poorly to the glass side it floats away. But the tissue which was surrounding it here remains and keeps the shape of these slices.
So here on this picture, these empty spaces are actually spaces from the filaments. And on this picture, they're filled yellow to help you orient yourself.
Now, you can see that there is a dark blue staining, multiple dots of dark blue staining. These are inflammatory cells which surround mesh filaments. So all dark blue staining which is labeled here is inflammation.
Another dye which is used in H&E stains proteins dark pink. This red areas is collagen. Collagen is fibrous tissue that ports a scar. And as you can see here, mesh filaments are surrounded by scar and by inflammation.

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These areas inside a larger hole in the mesh is irrelevant. There is more fluid, and when there's more fluid, you get ground substance, the portion of the scar is pushed apart and becomes more clear. So this is edema or swelling, that's how fluid on the tissue looks under the microscope.

BY MR. OSBORNE:

Q. All right. Let's take a look at your next picture.

MR. OSBORNE: And, for identification, your Honor, this is Figure 2. It has been marked J for identification.

THE COURT: And the title on it just so I can orient myself? I have copies here.

MR. OSBORNE: Yeah. It's "Mucosal Erosion Site," your Honor.

THE COURT: Thank you.

BY MR. OSBORNE:

Q. Dr. Iakovlev, explain to the jury what you identified in Figure 2.

A. As with previous picture, it's the same image. There are two copies. One copy is unaltered image, and the other copy has yellow

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filling in places where mesh filaments are or were, and labelling.

This site is the site where mesh went through the urethral wall and became exposed at the mucosal surface. This part here is squamous mucosa, it's urethral mucosa. This part is the wall of the urethra. And this place is where the mesh is closest to the explanted site. You can see there's a defect of tissue in the squamous mucosa or in the mucosa, and entire tissue is quite inflamed.

If you compare with previous picture where inflammation was mainly centered around mesh filaments, in this case the entire tissue is inflamed because there's an opening, it's like an open wound, and the bacteria and infection from the lumen from urethra could enter, and then the area became infected. And these inflammatory cells, these all little dots, came to the area to fight the infection that has caused open wound.

Q. All right. Dr. Iakovlev, let's take a look at your next photograph. We have five in total that we're going to look at. This will be

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the third.

MR. OSBORNE: Your Honor, this is Figure 7B titled "Thick Bundles of Urethral Muscle Under Mucosa, Smooth Muscle," and it's been marked as K for identification.

THE COURT: Thank you.

BY MR. OSBORNE:

Q. Explain to the jury, Dr. Iakovlev, what we see on Figure 7B.

A. This is the more sophisticated type of staining. When a mouse or a rabbit had smooth muscle, human smooth muscle proteins introduced in the body, and the immune system of the animal developed antibodies to fight with this foreign protein. And then we can extract these antibodies from the animal, label them with brown color and apply to the tissue, and then smooth muscle becomes brown in the sections.

Normal human body will have two types of muscles, striated and smooth. Striated muscle to control it like at will --

THE COURT REPORTER: I'm sorry. I'm sorry. The last sentence again?

THE COURT: I didn't hear after the

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two kinds of muscle.

A. Two kinds of muscles, striated and smooth. Striated muscle is muscle which we'll control like at will. If -- it's movements we do.

And smooth muscle is internal organs. It's our stomach, it's blood vessels, it's bladder and urethra. So this is smooth muscle which we do not control by our own will, which contracts on its own by the separate parts of our neural system.

In these pictures, there is two copies of the same as before. One is unlabeled, and the other one is labeled. There's squamous mucosa, which is urethral mucosa at the location of the surgery, and there are thick bundles of smooth muscle. This is the muscle which contracts urethra and controls contraction of the urethra. So these tissue comes from the tissue which was adherent to the mesh, and by this stain, we can see that adherent tissue to the mesh was part of the urethral wall, together with the mucosa.

BY MR. OSBORNE:

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Q. All right. Dr. Iakovlev, just a couple more.

Let's take a look at --

THE COURT: Just one moment.

BY MR. OSBORNE:

Q. Let's take a look at Figure 7C, "Urethral Muscle at the Erosion Site Against Smooth Muscle."

MR. OSBORNE: Your Honor, it's been marked for identification as L.

BY MR. OSBORNE:

Q. Again, Dr. Iakovlev, just to remind you to keep your voice up as much as possible.

A. And may I show Figure 2 at the same time?

Q. Sure. First off, explain to the jury what is on Figure 7C.

A. Figure 7C contains the same site as you saw on this photograph; however, staining is used for smooth muscle. So it's sections which was taken deeper. Next slice in the block from the same area as here, but the staining was used to highlight smooth muscle. So this is the site which is here. That's exactly the same.

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And on this photograph, you can see squamous mucosa here, defect, cross-section of the place where mesh filaments were, and then smooth muscle. So this demonstrates that the erosion site was at the urethral -- through the urethral wall.

Q. All right.

MR. OSBORNE: And then lastly, your Honor, it's our last photograph, it is from Figure 8. It has been marked for identification as M.

BY MR. OSBORNE:

Q. And, Dr. Iakovlev, please explain to the jury what your findings were in terms of Figure 8.

A. Figure 8 is a very high power magnification of a filament. This is taken with objective which magnifies it to 100 times, and there's another optics which magnifies it another ten times. It's 1,000 times magnification. It is the highest magnification light microscope can do. There is also oil between the glass slide and the objective, because otherwise you cannot achieve this

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magnification. So this type of magnification was 100, objective with oil immersion.

The pictures are split into upper panel and lower panel. Upper panel is regular transmitted light, so regular light we see. The lower panel is the polarized light. The polarized light we discussed earlier. This is the light photographers use on the lenses to reduce glare, or sometimes we have sunglasses which reduce glare as well. So this is polarized light.

The mesh filaments are surrounded by a layer. It's like a sheath or like a tree bark which absorbs histological dyes. You can see it is different from this core. The material peels off and has cracks. So each filament is surrounded by a dark -- or a sheath of degraded polypropylene which cracks and peels off, and it follows each filament.

In these photographs, you can see that this material is different from the non-degraded core, because non-degraded core is completely solid, doesn't have pores which can retain histological dyes. And to stain fabric, there

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are little pores where the dye is trapped.

In this case, this material is solid, and the dye cannot stain inside. This material has micropores where dye molecules can get trapped. It's why we can see it's dark purple. So this slide indicates that this is porous, this is non-porous. In this case, the long chains of polypropylene are broken down, and there are microcavities in it.

Then the next step for me was to see if this -- this layer is, in fact, polypropylene, and I examined it in polarized light. We use polarized light in pathology to identify foreign bodies. Foreign bodies which are clear, they become really bright like this one. You can see the difference. This is clear, and this is bright. All the ground becomes dark. Human tissue becomes dark because they do not polarize light as a foreign body.

In this case, polypropylene polarizes light, we can see it, and the bark which is peeling off is also bright. So this finding indicates that this bark is, in fact, polypropylene.

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Q. Did you also bring the slide itself which contains the piece of degraded mesh seen in photo 8?
A. Yes, I did.
Q. And would showing the jury the slide itself further assist you in demonstrating the degrading?
A. Yes, this will give some better understanding of how polarization works.
MR. OSBORNE: Your Honor?
THE COURT: Yes, the witness may do so.
How do you intend to do that?
MR. OSBORNE: He's going to project it right up onto the screen.
THE COURT: All right. Would you move the easel, please?
MR. OSBORNE: Yes.
BY MR. OSBORNE:
Q. Do you want to come down to the microscope, Doctor?
MR. OSBORNE: Is there a way to turn the lights down?
BY MR. OSBORNE:

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Q. Would that affect you, Doctor?
A. Yes, it will be better to see with dim lights.
Q. So explain to us, Dr. Iakovlev, what we're looking at here that's now up on the screen that you're seeing through the microscope.
A. When we examined first tissue --
Q. Again, keep your voice up, sir, if you can.
A. When tissue is initially examined, we see it in regular light. This is the picture what we see in regular light. And as I described before, the filaments are clear, we do not see it, it disappears. But the degraded material absorbs dye, and we can see it.
Another interesting feature is the outer layers, the surface of the degraded material absorbs more dye because there are larger cavities, and they trap more dye. The deeper layers are lighter because the cracks, the microcavities, are smaller, so there's less dye, and the color is not as intense.
Then I can examine the same section in

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polarized light, and polypropylene becomes bright, you can see it, both the degraded part and non-degraded part. And if I zoom out, you can see that the human tissue is dark, you cannot see it. All foreign material is bright. This is foreign material, this is foreign material, these little specs are foreign material, but the tissue on the background is dark.
Another feature which I can demonstrate from the same images as we saw before, which you saw on the posters, this is the same area. These are the mesh filaments, the fibrosis which is bridging from one filament to another, there is continuous fibrosis, the dense inflammation around the filaments, and the edema in larger compartments or larger holes inside the mesh.
Q. Thank you, Dr. Iakovlev.
THE COURT: For identification, the slide that is currently being projected is?
THE WITNESS: Right now, this would correspond to 1, picture 1, and initial polarization to picture 8.

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THE COURT: 8 for identification?
MR. OSBORNE: It is picture 1 which I believe is 1A, which is I for identification, your Honor.
THE COURT: I for identification?
MR. OSBORNE: I for identification. And corresponds to picture 8.
THE COURT: Right. Thank you.
BY MR. OSBORNE:
Q. Dr. Iakovlev --
MR. OSBORNE: Your Honor, can Dr. Iakovlev return to the witness stand?
THE COURT: Yes, of course.
THE WITNESS: Thank you.
MR. OSBORNE: And can we approach, your Honor, briefly?
THE COURT: Yes.
(Sidebar.)
THE COURT: Just try to speak into the microphone. I guess the battery has been fixed.
MR. OSBORNE: Dr. Iakovlev has a study he has done that he has looked at various pieces of polypropylene that is being presented in October and has been accepted by the

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International Conference of Incontinence, and I was going to ask him questions about this. Ms. Murphy has some objection, so I wanted to get the Court's guidance.

MS. MURPHY: Your Honor, what has been presented to me is represented as an abstract, but it has no publication indicated on it, there's been no presentation of its reliability, it is written by Dr. Iakovlev himself, and it's inappropriate under the case law of Bucida versus O'Toole and others, Sneed, to be used to bolster a witness's testimony. It's not been noticed as a medical treatise.

MR. OSBORNE: Your Honor, our response is that this goes to foundation in terms of his opinions. He's already established that he's looked at other pieces of polypropylene mesh in order to do that.

THE COURT: And the source of the mesh, he's already testified it was just collected from St. Michael's.

MR. OSBORNE: St. Michael's and other lawsuits and sent in by Dr. Bendavid. He's already testified to the basis of that.

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THE COURT: The document itself is not admissible, or reading from the document, but he can testify as to his personal experience.

MS. MURPHY: I think he's already done that. My issue was with the document itself.

THE COURT: Right.

MR. OSBORNE: Are you about to publish -- actually, he's already published online. Have you recently published a study on your work? Yes. Can you tell us about it? And what were his conclusions.

THE COURT: That's when you cross the line.

MR. OSBORNE: Okay.

THE COURT: He can testify, and to the extent that he has testified, but it is permissible for him to testify as to his personal experience examining mesh.

MR. OSBORNE: Okay.

MS. MURPHY: Thank you.

(End of sidebar.)

BY MR. OSBORNE:

Q. Now, Dr. Iakovlev, based upon your review of the records and slides in this case, do you have an opinion to a reasonable degree of medical certainty as to what caused the damage to Mrs. Cardenas's urethra?

A. After my review of clinical records and pathology specimen, my opinion that to a reasonable degree of medical certainty, the internal properties of the mesh and alterations of the structure of the mesh, together with changes in the tissue surrounding the mesh caused erosion of the mesh through urethral wall.

Q. And pathologically were you able to rule out other causes in this case?

A. Yes. Because when specimen came to me, I examined it for presence of non-mesh-related pathology. I didn't find evidence of neoplastic process, which are tumors. I don't see cancer in there, neither carcinoma from epithelium, or lymphoma from inflammatory cells, or sarcoma from soft tissue. I also don't see evidence of systemic disease like vasculitis which could cause damage of the tissue. All changes I saw, they were directly related to mesh in the tissue.

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Q. And based upon your review of the records of the slides, do you have an opinion to a reasonable degree of medical certainty as to what caused the erosion?

A. Yes. As I said, that internal properties of the mesh, changes in the structure of the mesh, and associated changes in the tissue caused erosion of the mesh through the urethral wall.

MR. OSBORNE: Thank you very much. No further questions.

MS. MURPHY: May I proceed, your Honor?

CROSS EXAMINATION

BY MS. MURPHY:

Q. Good afternoon, Doctor. How are you?

A. Good. Good afternoon.

Q. I'm going to provide you with a folder of some materials, with the Court's permission, in the event we need to look at your pathology report or other reports that you have (handing).

A. Thank you.

Q. If we could, Doctor, I'd just like to start with some general questions for you.

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I think you described that your position at St. Michael's and in academia is as an anatomic pathologist?
A. Yes.
Q. And currently you're also, I think, the director of the division of cytopathology?
A. Yes, I am.
Q. And would you say that your day -- or your duties and responsibilities are evenly split between anatomic pathology and cytopathology?
A. Cytopathology is a part of anatomical pathology.
Q. Okay. But your duties and responsibilities with regard to being division director. I guess I wasn't clear.
A. And as a division director, yes, I spend about 10 percent of my time for management.
Q. And you described earlier how you have some peer-reviewed publications in the area of pathology?
A. Yes.
Q. And you have no publications in the

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peer-reviewed literature on general polymer science, would you agree with that?
A. I agree with that, I don't have.
Q. And you're not a materials scientist, correct?
A. It is correct, I am not materials scientist.
Q. And you don't have any training or experience in -- specifically with regard to the materials for implantable medical devices, correct?
A. I have training within the field of anatomical pathology, because implantable devices are taken out of human body, and everything which is taken out of human body is submitted to pathology department.
Also, as pathologists, we perform autopsies of medical cases. In these cases we have students investigate the cause of death, and some patients die with some implantable devices, so we think -- the practice of implantable pathology, I had training and experience with implantable devices.
Q. Doctor, would you agree with me that

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your experience with mesh devices began when Dr. Bendavid contacted you in 2012?
A. Yes, I would agree with that.
Q. And that your experience with transvaginal mesh implantation devices began in 2013 when you got involved in litigation?
A. I received transvaginal meshes. First time I received transvaginal meshes in 2013, this is correct.
However, about the same time I received specimens from St. Michael's Hospital as well as from litigation --
Q. Okay.
A. -- cases.
Q. So your experience with transvaginal mesh, then, started in 2013, whatever the source it was, 2013?
A. Early 2013.
Q. Okay. And you are not a member of any professional organizations that concern polymers or the development of polymers, correct?
A. This is correct.
Q. And that's what we're talking about when we talk about the polypropylene mesh, we're

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talking about a polymer?
A. I have to expand on that question. I mean yes, it is made out of polymer, but polypropylene mesh is a medical device.
Q. And, Doctor, going back in your education and training, you are not certified or currently practicing as a surgeon, correct?
A. No, currently I'm not practicing as a surgeon.
Q. And so any training that you have with regard to surgery goes back to residency, would that be fair to say?
A. Yes. Last time I was involved in surgery service was in residency --
Q. You would --
A. -- as a surgeon.
Q. From time to time, do you find yourself in the operating room in order to accept a specimen or make some observations during a surgical procedure?
A. Yes, from time to time -- well, every week I attend operating room.
Q. Okay. Doctor, based upon your position as an anatomic pathologist, and based

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upon your background, you would agree with me that all surgery has risks?
A. Yes, all surgeries have specific and nonspecific risks.
Q. And all pelvic surgery with or without mesh would have risks attendant to it?
A. As any surgery, pelvic surgeries would have risks.
Q. And would you agree with me, Doctor, that one of the risks or side effects or complications, whatever word you want to use, is the formation of scar tissue related to surgeries?
A. Scar tissue, as I explained earlier, is a nonspecific response of foreign body. Any damage of the tissue will cause scarring. Surgeries are designed to minimize this effect, and in cases of implantable materials the degree of damage is larger than compared to the surgeries without the implantable materials due to specific implant/body interactions.
Q. Okay. But my question was just talking about surgery in general. We're talking about your experience that goes back to

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residency. But what you've just spoken of is that weekly you attend to the operating room.
So my question is simply that; does surgery raise a risk, pose a risk of the development of scar tissue?
A. Yes, it does.
Q. And it poses the risk of the development of scar tissue both internally wherever the surgery is being performed and at the site of the incision, wouldn't that be correct?
A. The very superficial layer, which is epithelium, heals without scar because epithelium can regenerate. The deeper layers, soft tissue, becomes scarred.
Q. And so that scar tissue to some degree, or that fibrotic reaction, is anticipated when there has been some sort of a trauma related to surgery, correct?
A. Yes, it is anticipated.
Q. And would you agree with me, Doctor, that scar tissue is normal tissue with normal structures within it?
A. Scar tissue is not normal tissue.

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Scar tissue is a repair tissue.
Q. Okay. It's a reparative tissue, and it contains blood vessels?
A. It does contain blood vessels.
Q. And it contains nerves?
A. It contains nerves.
Q. Doctor, in this case, have you reviewed the directions for use for the Obtryx?
MR. OSBORNE: Objection, your Honor.
THE COURT: And the basis?
MR. OSBORNE: Outside the scope of direct.
THE COURT: Under the Mass Rules of Evidence, I'm going to permit it.
THE WITNESS: Do I answer?
THE COURT: Yes, please.
BY MS. MURPHY:
Q. Let me put the question again, Doctor.
Have you reviewed the directions for use for the Obtryx?
A. I reviewed some manuals. I don't remember exactly if it was Obtryx. But yes, I reviewed manuals for surgeries for implantation of sling devices.

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Q. Doctor, I've put up on the wall there a page from the directions for use for the Obtryx. Under "Precautions," it states, "Do not use any mechanical means of contact with the mesh (such as clips, staples, etcetera) within the urethral support region of the mesh as mechanical damage to the mesh may occur."
Do you see that?
A. Yes, I do see that.
Q. Have you read that portion of the Obtryx directions for use prior to just now?
A. I don't remember. I cannot say.
Q. Would you agree with me, Doctor, that as a precaution, it's certainly prudent to put a precaution that says do not use any mechanical forces on the mesh during the course of implantation as damage to the mesh may occur? Would you agree with that?
A. I'm not clear about the statement. I mean, mesh needs to be handled during surgery, so it's mechanical force.
Q. But they're talking about clips, staples. Are the clips and staples other metals --

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A. Yes.
Q. -- made of some sort of a metallic?
A. Yes, I see that.
Q. Okay. And so is it appropriate for there to be a precaution that says some sort of a metal should not be used as mechanical damage to the mesh may occur?
A. It seems to be logical, yes, I would agree.
Q. Okay. And, Doctor, you understand through the course of your education, training, and experience that polypropylene has been used in various parts of the body for various applications for 50 or 60 years?
A. Around 50 years, late '60s.
Q. And polypropylene mesh has been used for a significant period of time in the repair of hernias?
A. Yes.
Q. And that was part of the project or research that you were doing with Dr. Bendavid, correct, that was on hernia mesh?
A. That's correct.
Q. And would you agree with me that even

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before you got involved in evaluating hernia mesh, explanted hernia mesh with Dr. Bendavid, explanted hernia mesh had been researched or studied microscopically for a long period of time?
A. I wouldn't agree with that, because what I found was a significant gap in science. Most of the studies were done on animal specimen, and recently it has been raised that most of the conclusions are based on animal studies.
In fact, the study -- very recent study identified that 50 percent of the explanted meshes from humans are being discarded without examination, and then a large proportion of those which are being examined are examined just grossly, so they look at them and there's no microscopy. A small proportion is done using microscope to investigate further, and very small proportion was done with a higher degree of details describing the specimens. Sometimes I receive specimens --
Q. Well, Doctor, 50 percent -- it's your understanding that 50 percent of the explanted

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hernia mesh is evaluated and 50 percent is not, correct?
A. 50 percent is completely discarded without evaluation, and only a portion of the remaining 50 percent receives microscopy.
Q. Well, I'm just going to take it in baby steps.
So 50 percent is discarded and 50 percent is examined, correct?
A. Yes.
Q. And of that 50 percent, a small portion, according to you, is evaluated under the microscope?
A. Yes.
Q. And that has been happening up until you and Dr. Bendavid decided to do more of the microscopic evaluation of the hernia mesh?
A. It's happening now. It's just regular routine at this stage.
Q. And that's new?
A. What is new?
Q. The fact that more of it is being evaluated is a new phenomenon?
A. I don't think more of it is being

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evaluated.
Q. Okay.
A. Yes.
Q. Doctor, is it your understanding that the polypropylene that's in the Obtryx is a macroporous mesh? Yes or no.
A. It depends on what classification we use for micro and macroporous.
Q. Okay. So you can't answer my question?
A. If we use one specific classification, then we can define. But we have to look at -- there have been several classifications offered.
Q. Okay. Would you agree that it's monofilament?
A. It is monofilament, yes.
Q. Doctor, you did a whole discussion with Mr. Osborne about the degrading of the polypropylene. Would you agree that while you may have seen that, the clinical relevance of degradation remains unclear?
MR. OSBORNE: Objection, your Honor.
THE COURT: Well, he may indicate whether he agrees with that statement or not.

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And the jury shall disregard the introduction to the question.
A. It's not a simple answer.
BY MS. MURPHY:
Q. Okay. Well, let me try it again for you, Doctor.
Would you agree with me that the clinical relevance of degradation of polypropylene remains unclear? Yes or no.
MR. OSBORNE: Objection, your Honor. Sorry. Objection, your Honor.
May we approach?
THE COURT: Yes.
(Sidebar.)
THE COURT: Under Mass, the order of proof, the cross examiner isn't limited to the scope of the direct, but anything that's inquired about can be followed up on redirect.
MR. OSBORNE: Thank you.
Prior to his examination, we spent lots of time talking about the fact that I would not take him into clinical boundaries, and by agreement purposely didn't do that, limited his conclusions to the pathology and his conclusions

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from the pathology. Now it's like I get bootstrapped, can't ask --
THE COURT: No, you're not. Basically, it was precluded on direct, but anything that she inquires about on cross examination you may follow up on.
MS. MURPHY: Well, I am trying to follow up on the last series of questions that Mr. Osborne put to this witness, because he talked about the changes in the properties of the polypropylene being the cause of the erosion. Those changes, I would assume that the jury will conclude, will be the degradation about which he testifies. And he has previously testified, Volume 1, Page 431, that the clinical relevance of degradation remains unclear. And I think that just the fact that he said that -- trust me, I'm not going to go through the clinical issues -- but he has drawn a conclusion on his direct that I'm going to cross examine him on as to the relevance.
THE COURT: But you can't -- assuming that you confine him to a yes or no answer, Counsel then is entitled to ask him about that

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question and answer, and if he wishes to elaborate on it, he may.
MS. MURPHY: Well, I think, your Honor, I am being confined here by the fact that I can't -- he just gave a clinical opinion that this is what caused the erosion. That's a clinical opinion. Now I should be able to impeach him with a statement that he made previously in a deposition.
THE COURT: And then Counsel is entitled to have him explain whether there is any inconsistency.
MS. MURPHY: Fair enough. Yes, that I understand, your Honor.
MR. OSBORNE: Thank you, Judge.
(End of sidebar.)
THE COURT: Dr. Iakovlev, if you could, just listen to the question that Counsel puts to you and answer the question that is asked, and then Mr. Osborne will have an opportunity to inquire again.
THE WITNESS: Thank you.
BY MS. MURPHY:
Q. My question is, again, Doctor, would

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you agree with me that the clinical relevance of degradation is not clear? Do you agree with that statement?
A. Not entirely. There are some features which we know, and there are some features which still need investigation. Unclear definition means we just don't know, but we do know some parts.
Q. Doctor, as part of your education, training, and experience, would you agree with me that you are not familiar with testing standards for medical devices?
A. As I mentioned, I'm not materials scientist.
Q. Okay. And I'm just going to again go baby steps through this a little bit, Doctor.
So you're not familiar with the standards of the American Society for Testing and Materials, is that correct?
A. It is correct.
Q. And you are not familiar with the ISO standards?
A. It is correct.
Q. And you are not familiar with any

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internal Boston Scientific standards for testing of materials, correct?
A. It is correct.
Q. I would like to talk about -- I would like to talk about the process that's involved in -- a little bit in general, but more so specifically in this case -- of getting a specimen from a surgical location to the pathologist. Okay? And would you agree with me that there are a number of steps involved in that process?
A. Yes.
Q. Okay. Doctor, do you understand that the mesh was removed by Dr. Childs in January of 2011?
A. Yes, that's what the pathology report and operative report states.
Q. And you've reviewed these documents, the operative report and the pathology report?
A. Yes.
Q. And do you see that Dr. Childs describes that he dissected down onto the urethral sling and identified the structure, correct?

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A. Yes.
Q. And then he dissected out along the sling in either direction and sharply excised an approximately 2-centimeter segment of the sling, is that correct?
A. This is correct.
Q. And so you understand that that's how the mesh sling was removed by Dr. Childs?
A. Yes.
Q. And in order to do this removal of the sling, Dr. Childs describes "sharply excised." Do you know what instrument he used to sharply excise the 2-centimeter segment of the sling?
A. I don't know exact instrument, but it was cold, it's a cold dissection, not cauterized. The tissue is not burned during sharp dissection.
Q. Okay. So it was without cautery?
A. Without cautery.
Q. Okay. But the exact tool that Dr. Childs used in order to excise that segment of the sling you don't know?
A. I don't know.
Q. And you don't know what degree of

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difficulty Dr. Childs had, if any, in removing that 2-centimeter segment of the sling, correct?
A. No, I don't.
Q. And you don't know what force, if any, Dr. Childs needed to use in order to remove that segment of the sling, correct?
A. No, I don't. This is correct.
Q. And you know that, based upon your training and knowledge and based upon the operative note, that he did need to do some cutting in order to excise the sling, correct?
A. Yes, this is correct.
Q. And after he did that, he would need to grip that area of the sling with the tissue in order to remove it, correct?
A. Yes, this is correct.
Q. Do you know what instrument he used in order to grip it and remove the tissue, the mesh and the tissue?
A. No, I don't know.
Q. And you have no knowledge of the shape or size of the pores of that mesh while it was in Ms. Cardenas, do you?
A. It was in the range where I see in the

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microscope.
Q. Okay. After the specimen -- after the mesh was removed -- well, strike that.
You can't tell us to what extent, if any, Dr. Childs distorted the mesh in the process of cutting it and removing it, can you?
A. No, I cannot.
Q. And you don't know whether the process of cutting and removing the mesh by Dr. Childs cracked the mesh in the process of removal? You don't know one way or the other, do you?
A. I actually do, because I see the changes in all specimens, all my 130, and I --
Q. I'm talking about this one, Doctor.
A. That's my answer. Judging by knowledge and experience in examination of over 130 specimens, I see the changes in each specimen; therefore, it doesn't matter how it was removed, the changes are still there.
So for this specific case, I can say that the method of removal has no effect on the changes that I observe under the microscope.
Q. Okay. Doctor, would you agree with me that you don't know whether the process of

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removal that we've been talking about with Dr. Childs with the sharp instruments and the materials and tools needed to grip the mesh in order to remove it, you don't know whether those instruments are capable of cracking the mesh one way or the other, correct?

MR. OSBORNE: Objection, your Honor. Asked and answered.

THE COURT: No, different question. The witness may answer.

A. As I mentioned before --

BY MS. MURPHY:

Q. Is that yes or no, Doctor?

A. You have to repeat the question.

Q. I will give it my best.

Would you agree with me, Doctor, that you don't know one way or the other whether the process of removing the mesh, as we know Dr. Childs did in January of 2011, with the tools that he used to cut it, to grip it, to remove it, you don't know whether that process with those tools was capable of cracking the mesh in the process, correct?

A. I do know. As I mentioned, based

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on --

MR. OSBORNE: Your Honor, can the witness finish his answer?

THE COURT: On redirect he may explain his answers.

THE WITNESS: Can I continue?

THE COURT: Not at this time, sir.

BY MS. MURPHY:

Q. Doctor, in front of you in that folder that I handed you, you have a copy of your deposition -- I sure as heck hope the print is bigger than mine -- from January of 2014. I think there may be a couple of volumes.

A. Yes. Do you want me to pull it out?

Q. Yes, please.

Is that the January, 2014, January 14th?

A. Yes, January 14th, 2014.

Q. Page 423, please.

A. It's the wrong volume. Yes.

Q. On Page 423, if you start reading, Doctor, at line, I think it's 4, and go down to line 20 or 19, I just want you to read that to yourself.

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A. "Do you agree that the" --

Q. No, no. Just read that to yourself. I'm just giving you a second to familiarize yourself with it.

(Witness reviewing document.)

BY MS. MURPHY:

Q. Do you see, Doctor, that there was a discussion at your deposition about the removal process and its potential impact in creating cracks?

A. Yes. Yes, I do.

Q. Okay. And did you state that -- the question is "How can you be sure that the cracks that you observed were caused by that process?"

And your answer was "Some of them were, but not the -- the central part didn't crack."

Did you testify to that?

A. Yes.

Q. So there were some cracks that were not in the central part that were created as a consequence of this removal process. Would you agree with that?

A. No, this is not correct.

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Q. Okay.

A. The central part didn't crack at all.

Q. That's what I just said.

A. Well, some cracks -- I meant some cracks in the bark, in the degraded bark, so --

Q. Okay. So there were some cracks that were created in the removal process that we've been discussing in that outer layer that you've talked about?

A. Yes.

Q. Okay.

A. I meant that the degraded bark can crack --

Q. Okay.

A. -- either before removal, during removal, or after removal.

Q. Okay.

A. It's a different -- it has different properties than the central part.

Q. So the outer layer that you call bark -- and by the way, you're the one that coined that word to use for the outer layer of the polypropylene, didn't you? You testified that you decided to call it bark?

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A. Yes, I did, because I had a hard time to explain this, and when I said "bark," people suddenly understood me.
Q. So it's that outer layer that you were describing with cracks in it that may have cracked in this removal process, correct?
A. It cracked during the removal process because it could crack, the central part couldn't.
Q. Right. And I'm just asking about the outer part, Doctor, and that it may have cracked during the removal process, correct?
A. Some of those cracks could have been caused during the removal process.
Q. And, Doctor, after a specimen --
MS. MURPHY: Can we go to --
BY MS. MURPHY:
Q. After the specimen was removed by Dr. Childs, it was sent to pathology, correct?
A. Yes.
Q. And it's sent to pathology -- and you went over this a bit before, but it's sent to pathology in a jar in formalin?
A. Yes.

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Q. Okay. And would you agree with me, Doctor, that some formalin can be aggressive enough to cause degradation? Would you agree with that statement?
A. No, I cannot agree, because I conducted my experiments. I kept new meshes in formalin up to four months and did not observe the degradation bark.
Q. Doctor, do you remember testifying -- well, let me just show you.
There's a deposition, Doctor, dated July 14th, 2014, and it would be Page 153.
A. July 11th or --
Q. I think it's July 14th. July 14th.
MS. MURPHY: May I assist the witness, your Honor?
THE COURT: Yes.
BY MS. MURPHY:
Q. It's got much bigger print.
A. Oh, here it is. I found it.
Sorry, which page?
Q. Page 153.
A. Yes.
Q. And did you -- you were being asked

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about the effects of the pathology process on a specimen, and there was a question that said, "Any other possible cause that you took into consideration in coming to your opinion that you give in that paragraph on degradation?
"Answer: Yes."
Okay. And the first sentence, and I'll refer you to the full one, but the first sentence is "Formalin, can it form -- can it be aggressive enough to cause degradation? Yes."
Did you make that statement?
A. Seems to be --
Q. Did you make that statement, Doctor? Yes or no.
A. I don't remember making it this way. I couldn't answer yes. I mean --
Q. Okay. Well, let's try it this way.
Was your answer "Formalin, can it form -- can it be aggressive enough to cause degradation? Yes."
Did I read that correctly?
A. I think there is punctuation which was transcribed wrongly, because then it says, "Yes, I did testing."

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Q. Okay.
A. Because I think "yes" belongs to the next sentence.
Q. Okay. Once the specimen's in formalin, and in this particular case when it went to the lab at Alta View Hospital, it was initially grossly examined, correct?
A. Yes.
Q. And that's in part what we've got up on the board there, and the gross examination is basically just using your eyes to examine a specimen and give a size, I think you said?
A. Yes, that's correct.
Q. And what was grossly examined here is a piece of apparent plastic mesh with a small amount of attached pink-tan tissue, and it gives a measurement, correct?
A. That's correct.
Q. And then after that gross examination, according to the pathology report, the tissue was removed from the mesh, correct? Is that what the report at least indicates?
A. Yes, this report does.
Q. Okay. And you reviewed this report

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and understood that the tissue was being separated from the mesh, and the tissue was being thereafter processed, correct?

A. Yes, but not all tissue. When they say "tissue removed," it means that part of the tissue.

Q. Sure.

A. Just to be correct.

Q. I'm just trying to describe and see if we're on the same page. And that there was an attempt made by a person in the pathology department at Alta View Hospital to separate the tissue from the mesh, correct?

A. Yes.

Q. And then it was the tissue that went on for processing, placed into paraffin -- we'll go through this in a second -- and eventually made its way to you for your examination, correct?

A. Yes.

Q. And, in fact, that the mesh, once separated from the tissue, was put back in the specimen container, correct?

A. The usual way of grossing the

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specimens, when the tissue is hard or seems to be -- or it's going to poorly embed in paraffin, is being removed, and then all foreign objects or foreign tissue which contains foreign objects which is all together in one complex, this can be submitted, and this can go into paraffin. It's really hard to cut mesh without any inherent tissue because, as I said, it doesn't adhere to the glass slide.

So this statement cannot be taken figuratively that there are no mesh, because this is mesh without tissue which is visible which is sticking out like fishing line. That part was removed. Whether it was within the tissue we submitted, that's how I interpret it.

Q. Okay. But all I was trying to do was say that the gross mesh was separated from the gross tissue. Do we agree there?

A. There was an attempt to separate tissue which would be easy to embed and cut from the completely bare mesh which is difficult to cut.

Q. And then the mesh itself separated from the tissue, as best someone could do, was

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put back in the specimen container, and the separated tissue was then continued on in its processing, correct?

A. Yes, that would be --

Q. And do you know what instruments were used to separate the tissue from the mesh?

A. No, I don't know.

Q. Would it be scissors, or tweezers, or some kind of object like that?

A. Usually scissors or scalpel.

Q. Scissors or scalpel. Okay.

The mesh that went back in the specimen container, that's back into the formalin, or the container that had the formalin in it?

A. Yes.

Q. And that container never made its way to you for evaluation, correct?

A. I received only glass slides.

Q. Right.

So that would mean that that container didn't make its way to you, correct?

A. I don't know where that tissue went. If that tissue was re-embedded back into

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paraffin, it was in my slides. If it wasn't, it wasn't.

Q. Would you agree with me, Doctor, that the separation of the tissue from the mesh would distort the tissue using the scissors or a scalpel?

A. To a degree, yes.

Q. And would you agree that that process of separating the tissue from the mesh can lead to the creation of artifact once it's on the slide?

A. Yes, it can lead to some artifacts --

Q. And what --

A. -- but we can see the artifacts.

Q. And we'll get to that.

And what is artifact, Doctor?

A. Artifact is changes. If we want to make a definition of artifacts in histology slides, artifacts would be changes which occurred after the specimen was taken out of the body.

Q. Okay. And would you agree with me that that artifact is something that is a distortion that does not represent or reflect

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normal anatomy or pathology?
A. I wouldn't agree with that specific definition.
Q. Okay. But would you agree with me that artifact can be represented by empty spaces that you may have on your slides?
A. No, I wouldn't agree with this.
Q. Okay. Would you agree with me that the process of removing the tissue from the mesh that we've been talking about with either scalpel or scissors, that that -- the use of the scalpel or scissors has the ability to impact the mesh that the tissue is being removed from?
A. Sorry, it was a long question. Could you repeat it?
Q. I'm not sure I can, but let me try.
Would you agree with me, Doctor, that, again getting to this process of separating the mesh and the tissue as the pathology assistant was trying to do, you said it would be with the use of either scissors or a scalpel to do that?
A. Yes.
Q. Would you agree with me that the use of the scissors or scalpel can damage the mesh

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during that process? Yes or no.
A. Yes, cuts through it.
Q. Is the next step -- once the tissue is separated as best they could do, is the next step to put that tissue in the paraffin block?
A. No.
Q. Is the next step to dehydrate the tissue and to remove the water from it?
A. Yes.
Q. And then is that done by applying a series of alcohols that are in increasing concentrations?
A. Yes.
Q. Would you agree that the process of dehydrating the tissues with these alcohols can cause artifact in the process?
A. You have to define specifically what artifacts and what part of the tissue.
Q. Would you agree with me that the process of dehydrating with the series of alcohols can cause distortion of the tissue?
A. Tissue shrinks somewhat during, because water is removed, yes.
Q. And would you agree with me that it

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also may create spaces, which are a distortion?
A. During shrinking, some sizes are changing.
Q. And then is the next step in the process a clearing process to remove the alcohols?
A. No. That alcohol is substituted by xylene and paraffin, because it --
Q. And then are we at the paraffin level?
A. Then it goes into paraffin, yes.
Q. And once the tissue has been embedded in paraffin, I think you described this, it gets cut in very small slices, correct?
A. Thin slices, yes.
Q. Thin slices.
And what did you tell us was used, a mito --
A. Microtome.
Q. Microtome.
And how thin or how thick are those slices, Doctor?
A. Usually 4 microns. It can be anywhere from 3 to 20 microns. It's hard to see when the tissue gets thicker than 20 microns. Regular

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standard thickness is 4 microns.
THE COURT: Excuse me. It's just 1:00. Is this a good time to break?
MS. MURPHY: Sure.
THE COURT: All right. We'll take the luncheon recess until 2:00.
THE COURT OFFICER: All rise. Jury out.
(Jury not present.)
(Whereupon, a luncheon recess was taken at 1:00 p.m.)

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AFTERNOON SESSION
1:59 O'CLOCK P.M.

THE CLERK: Court. All rise, please.
THE COURT OFFICER: All rise. Jury entering.
(Jury present.)
THE COURT OFFICER: You may be seated. Court is in session.
THE COURT: Good afternoon, ladies and gentlemen.
And, Doctor, you're still under oath, sir.
MS. MURPHY: May I proceed, your Honor?
THE COURT: Yes, please.
MS. MURPHY: Thank you.
BY MS. MURPHY:
Q. Doctor, I just want to ask you a couple of questions about information you provided to us during your direct testimony.
Did you tell us that proteins under one or more of these stains will stain blue?
A. No, I don't recall that.

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Q. Okay. Would you -- let's try it this way.
Would you agree with me that proteins will stain blue?
A. By what dye?
Q. By your H&E stains?
A. No. Proteins stain pink.
Q. Pink. Okay.
You prepared a pathology report following your examination of these slides, correct?
A. Yes.
Q. I hope that you have a copy of it in that folder that I provided you, Doctor. Would you take a look? It might be easier. Or you can look at the monitor.
A. It's too small.
Yes, I do have it.
Q. Okay. And this is your report titled "St. Michael's Department of Laboratory Medicine."
And that's where you do your anatomic pathology and your psychopathology, correct?
A. Yes, that's correct.

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Q. Okay. If we go to the bottom, there's a section called "Synoptic Diagnosis."
Do you see that?
A. Yes, I do.
Q. And is that just a shorthand outline of what your findings were?
A. Yes, it's at least a feature of assessing all explanted meshes.
Q. Okay. And one of the things that you noted was gross mesh deformation, and you said you cannot assess, correct?
A. That's correct, because I didn't receive.
Q. And that's the gross, just looking at it, correct?
A. Yes. I received only slides.
Q. And then microscopic mesh deformation, you say that you cannot assess that because it's a fragmented specimen, correct?
A. Yes, that's correct.
Q. Okay. And that's fragmented because it was being separated -- the tissue was being separated from the mesh, correct?
A. No.

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Q. No? Okay.
You also note that acute inflammation was not significant. So your findings for acute inflammation were not significant to you, correct?
A. That's correct.
Q. Okay. And if we go to the next -- the second page, you have -- and I think you described this already under "Thickness." There's thickness, and then there's 4 --
THE COURT: If you could move back, I think you're in the sight line of the jurors.
MS. MURPHY: My apologies.
THE COURT: And is the podium still in your sight line? No.
BY MS. MURPHY:
Q. For thickness it's 4, and then symbols.
Is that a symbol for microns?
A. Yes, it is.
Q. Okay. So the thickness of the specimen that you described on the slide that was cut by the mito something, the knife --
A. Microtome.

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Q. -- is 4 microns, correct?
A. No. This number 4 means different measurement.
Q. Okay. So that's the thickness of what you consider to be the degradation part, the degradation bark?
A. Yes.
Q. Can you tell me, Doctor, how many microns, if you know, is like a human hair?
A. That would be difficult. It's different. It's not the same.
Q. Okay. Would it be in the range of 100 microns?
A. It would be smaller than 100 microns.
Q. More than 50?
A. I don't know.
Q. Okay. When you were talking about the pictures that you had here of the slides that you reviewed, in areas you noted that there was edema?
A. Yes.
Q. And you described that edema as being swelling, or that the tissue swelled?
A. Yes.

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Q. And would you agree with me that the -- it's fluid that is leaking that causes the tissues to swell?
A. Leaking from where?
Q. That there's an accumulation of liquid that causes the tissues to swell better?
A. Yes, accumulation is a better term.
Q. Okay. And does that liquid also contain protein?
A. Yes. All fluids will contain proteins.
Q. Okay. And would that be a protein like an albumen?
A. There will be some albumen as well.
Q. And by the way, you may remember this, but if not we can go back to the slide, but when you were looking at the operative report, you noted that the mesh sling that Dr. Childs removed he removed from the area of the mid-urethra, is that correct?
A. Yes.
Q. Doctor, at the time of your depositions in -- earlier in 2014, you testified that you were not familiar with the concept of

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the Vroman effect, is that correct?
A. That's correct.
Q. Do you remain unfamiliar with the Vroman effect?
A. Yes, I remain unfamiliar.
Q. Would you agree with me that polypropylene in general is hydrophobic?
A. Yes, I do agree.
Q. So as a general proposition, polypropylene will not absorb liquid?
A. In solid state.
Q. In solid state it will not absorb liquid, correct?
A. If it's porous, the pores within the material can entrap liquids.
Q. Okay. And again, as a general proposition, would you agree with me that foreign bodies do not absorb the stains that you use in your pathology examinations, as a general proposition?
A. No. I mean, there are different foreign bodies. Staining is -- there are different ways why dyes stain in the tissue. It can be chemical bond or it can be simple

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trapping in pores, in cavities. So different foreign bodies, depending on their nature, will stain by some stains, and will not stain by other stains. And some foreign bodies will not stain with any stain because they neither form chemical bonds, or they have enough cavities to trap dyes.
Q. Doctor, would you agree with me that you use stains and dyes in order to separate human tissue from non-human products?
A. It can be done with some stains, but generally, many stains will stain both human tissue, non-human tissue, and some non-biological objects. Again, it depends on type of staining, on mechanism of dye being connected to the tissue.
Q. Doctor, when you were testifying earlier, one of the points that you made was that the polypropylene that you saw in large measure was clear, correct, and you pointed that out?
A. Central parts of the filaments were clear.
Q. Okay. And you noted that in other

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areas where there were white circles or holes, that would -- that, in your opinion, represented a location where polypropylene is or was, is that correct?
A. Some of those spaces, yes.
Q. Okay. And would you agree that some of those spaces are artifact?
A. The rounded, oval spaces, I pointed they were spaces from filaments. Generally, there can be some defects in the tissue to be clear.
Q. Okay. And would --
A. It depends on the hole.
Q. And some of those defects are created as a result of the tissue being pulled from the mesh and the tissue processing, would you agree with that? Yes or no.
A. I can't answer it simply, because you have to point to the space, and then I can tell you what it is.
Q. And we'll get there.
Doctor, one of the things you testified was that the polarization test, that polarized light you were talking about,

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separates human tissue from foreign body?
A. It can be used. It doesn't separate all foreign bodies from human tissue, but those which are clear and can polarize light, they become visible in polarized light.
Q. And that's what you were talking about, that the foreign body -- what you said was the polypropylene in the bark area became bright. Did you testify to that?
A. Yes.
Q. And that human tissue would go black, correct, under the polarized light?
A. Yes, much darker than polypropylene.
Q. Much darker.
Doctor, in addition to the representations you went over with Mr. Osborne, you provided additional pages as part of your report. I believe you should have them with you. And I'm asking you to look at Figure 1B.
A. Yes, I do see it.
Are you referring to supplemental?
Q. I am, Doctor, yes.
A. Yes.
MS. MURPHY: And so if I may approach,

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your Honor?
THE COURT: 1B is J for identification?
MS. MURPHY: I don't think it got marked, your Honor.
MR. OSBORNE: No, it did not get marked. 1B is not marked.
MS. MURPHY: 1B is not marked.
THE COURT: Oh.
MS. MURPHY: 1A, I believe.
MR. OSBORNE: Correct. In sequence, it would be N.
MS. MURPHY: If I might just approach?
BY MS. MURPHY:
Q. Is this what you have? Yes.
A. Yes.
Q. And, Doctor, is that representative of the 1B that you provided with your supplemental report?
A. Yes, that's picture 1B.
Q. And the bottom -- the top pictures you represent are slides that you reviewed relating to Ms. Cardenas, correct?
A. That's correct.

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Q. And the bottom part is an example that you took from a textbook, correct?
A. From a review article.
Q. From a review article.
MS. MURPHY: And if we could pull up the title of that review article, that bottom writing.
A. Or it could be --
BY MS. MURPHY:
Q. Well, we'll pull it up. I'll show it to you, Doctor.
A. Because reviews use original articles.
Q. Okay. So this is from Lefranc, et al.?
A. That's review article, yes.
Q. And that picture, which is called a microphotograph, had certain findings within it which you've described, correct?
A. That's correct.
Q. Okay.
MS. MURPHY: And if we could pull the picture up again, please.
BY MR. MURPHY:
Q. And what you were representing, using

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this photograph from a medical article or scientific article, is that there was loose connective fibroadipose tissue represented in that photograph, correct?

A. Yes.

Q. And that there were fibrous capsules around the filaments, and that was represented from the photograph in the article, scientific article, correct?

A. That's correct.

Q. Okay. And this is the photograph that you used, Doctor?

A. It's similar. Maybe this one. Depends on if I took it from -- looks like the same, because this one is black and white. I don't know why it's black and white.

Q. So this is the picture that you turned into a color representation?

A. No, I didn't turn it into color. I think I took it color already.

Q. Let me back up.

Mine is probably Xeroxed black and white. Yours was probably color, correct?

A. Yes.

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Q. I beg your pardon.

So you took what was a color photograph in the article that you referenced, and you used it as an exemplar to make a certain point with regard to Mrs. Cardenas's slides, correct?

A. Yes.

Q. Okay. And the photograph that you used described that it was -- achieved tissue differentiation within the mesh without fibrous encapsulation. Is that what appears under the photograph that you took --

THE COURT: You have to back up, Ms. Murphy.

BY MS. MURPHY:

Q. Is that what is written under the photograph that you took to use as an exemplar to make a certain point about Ms. Cardenas's tissue pathology?

A. Yes, that is written on the picture.

Q. Okay.

MS. MURPHY: Thank you, Doctor. I don't have anything else for you.

THE COURT: Would you just check,

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because I have that marked as J for identification, that slide.

MS. MURPHY: I don't think we have that marked. I would like to mark it, however. At least, I don't have it blown up.

MR. OSBORNE: 1A is J, your Honor. That is 1B. So there's 1A and 1B.

THE COURT: I thought 1A was I.

MR. OSBORNE: I'm sorry, you're correct. 1A is -- I apologize, it's I.

THE COURT: And 1B?

MR. OSBORNE: 1B was not marked in the sequence.

THE COURT: All right. Let us mark it then. What is J? Or did I just anticipate we would be marking it?

MR. OSBORNE: J is Figure 2.

THE COURT: Okay.

MR. OSBORNE: That was the confusion. 1A, then it goes 1B, then 2.

THE COURT: Okay. So would you just mark 1B?

MS. MURPHY: I would like to mark 1B for identification.

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(Whereupon, Exhibit Number N, Blow-up of photograph of Table 1B, was marked for identification.)

THE CLERK: It will be N, your Honor.

THE COURT: Thank you.

MS. MURPHY: And if I might also offer the representation from the article that Dr. Iakovlev mentioned.

THE COURT: Could you show Mr. Osborne?

MS. MURPHY: (Handing).

MR. OSBORNE: No objection.

MS. MURPHY: Thank you.

THE COURT: For identification?

MS. MURPHY: For identification, yes.

THE CLERK: That will be O, your Honor.

(Whereupon, Exhibit Number O, Representation from article, was marked for identification.)

MS. MURPHY: Thank you.

REDIRECT EXAMINATION

BY MR. OSBORNE:

Q. Dr. Iakovlev, in your practice, do you

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have personal experience looking at explanted transvaginal mesh specimens for degradation?
A. Yes, I record presence of degradation layer in each specimen, and I measure it, as we saw in synoptic summary.
Q. Tell us about that experience. How entailed has it been?
MS. MURPHY: Objection.
THE COURT: He may describe his experience.
A. I see degradation layer in 100 percent of specimens. The thickness is different, that's why I measure it, but I see it in each single specimen, regardless if it's transvaginal, interior abdominal wall, or inguinal hernia mesh.
BY MR. OSBORNE:
Q. And that's approximately out of how many specimens?
A. Approximately 130 specimens. That's pertinent to monofilament polypropylene meshes.
Q. Now, how do you know the degradation that you saw in those meshes wasn't caused by removal or handling?

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A. As I mentioned, that I observed degradation layer in all specimens. These specimens are manufactured by different manufacturers, and they are implanted in different sites. There are different techniques of removal of them, and I see -- still see 100 percent of specimens having -- showing this layer of degradation.
Q. How does inflammation also help you make that determination in terms of whether or not the degradation is caused outside the body or inside the body?
A. There are several features which made me conclude that degradation happens inside the body. The first feature was observed in the specimens which were removed with tools which heat up tissue, cauter it. These tools, they use heat to separate tissue. Tissue is burned around, and then it is separated. The degree of heating is so high that some polypropylene melts, and I see the melting of the bark at the edges of the specimens. There is no way this could happen after. The cautery happens during the excision; therefore, bark existed before the

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excision.
More, the bark melts together with non-degraded, central core. They all melt together and form common pool. They're the same material. When the tissue is heated up to the degree, both the bark and the central core melt together and form one single pool of melted material. This was observation in light microscopy.
I also conducted electron microscopy. In electron microscopy, I see the same layer of bark, which is, as I described, looks like a bark or like a sheath around filaments, it's about 4 microns thick. And I found the live cells which made it into the crack, expanded the crack, and remained wedged into the crack. The cell needs to be alive just to make it into the crack and expand it. This proves that the cracking of the bark happened in the body, because otherwise, the cell couldn't make it into the crack and expanded this way. So these two features prove that degradation happened in the body, in vivo.
Q. Now, do you have an opinion to a

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reasonable degree of scientific certainty as to whether Dr. Childs's removal or handling of the mesh caused the mesh to degrade in this case?
A. My opinion, to a reasonable degree of medical certainty, that removal did not cause degradation of polypropylene.
Q. And what is that opinion based upon?
A. It's based upon my experience and my testing of polypropylene meshes, and my experience in examining explanted polypropylene meshes from the human body.
Q. You were also asked some questions about the effect formalin can have on polypropylene.
Do you recall that?
A. Yes.
Q. Okay. Have you actually studied the effect formalin can have on polypropylene transplanted mesh -- let me ask you a better question.
Have you actually studied the effect formalin can have in terms of causing degradation or explanted polypropylene mesh?
A. Yes. This question was very important

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to answer, because some specimens remain in formalin only for 24 hours. Those specimens I saw in St. Michael's Hospital. They were in formalin only 24 to 48 hours. Many of the specimens, which are processed in normal way, they're put in paraffin within 24 to 72 hours, but some specimens remain in formalin for two years or longer. Therefore, it was important to rule out that degradation is caused by formalin.

What I did, I took samples of brand-new meshes of at least two different manufacturers and put them in formalin, and then with an interval of one week, two weeks, and four months, the meshes were taken out, they were put in the same cassettes as we put the specimens, then they were put in the same machine going through all the dehydration, paraffin embedding procedures, and then stained as all other specimens, as the specimen of our patient here. However, I did not observe bark at either interval. Even after four months in formalin, there were no detectible bark on the filaments.

Q. So did formalin cause any degradation

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of the polypropylene mesh in this case?

A. No. Based on my testing, I can say no.

MR. OSBORNE: Thank you, your Honor. No further questions.

THE COURT: Do any of the jurors have a question for the witness? No.

All right. Thank you, sir. You may step down.

MR. MONSOUR: Your Honor, while he's working on that, during opening several documents from the admitted list, agreed-upon admissible list were shown to the jury. I would like to go ahead and offer them into evidence at this point in time.

THE COURT: If you could just state for the record what the item is.

MR. MONSOUR: The first document is a Boston Scientific document, it's titled "2 Civ, Coated Mesh Files from Patrick Antel." There's no date at the top, but on the bottom it says, "On August 3rd of 2007," and I would like to offer that one into evidence.

THE COURT: It will be the next

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number, please.

THE CLERK: It will be Number 16, your Honor.

(Whereupon, Exhibit Number 16, Document title Coated Mesh Files from Joseph Antel, was marked in evidence.)

MR. MONSOUR: The next article, your Honor, is dated -- or on the top right is stamped August 23rd, 1998. At the top it says, "New Urology ProteGen Sling."

THE CLERK: That will be 17, your Honor.

(Whereupon, Exhibit Number 17, Article titled New Urology ProteGen Sling, was marked in evidence.)

MR. MONSOUR: The next document is the Clinical Risk/Benefit Analysis of the Obtryx Sling System. There are several dates on it. It's -- on the last one, it says, "Date: Second update, July 12, 2004."

THE CLERK: Exhibit Number 18, your Honor.

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(Whereupon, Exhibit Number 18, Clinical Risk/Benefit Analysis of the Obtryx Sling System, was marked in evidence.)

MR. MONSOUR: The next document is entitled -- it's called "Meshology 101: Summer Training Conference, August 3rd, 2004." There are redactions to the document, which I believe are all appropriate, but I'll let Mr. Anielak double-check.

THE COURT: That's going to be 19?

THE CLERK: Yes, your Honor.

(Whereupon, Exhibit Number 19, Document titled Meshology 101: Summer Training Conference, August 3rd, 2004, was marked in evidence.)

MR. MONSOUR: The next document, your Honor, is a United States patent application publication, Publication Number US 2011/0184228A1, publication date July 28, 2011.

THE CLERK: Exhibit Number 20, your Honor.

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(Whereupon, Exhibit Number 20, 7/28/11 United States Patent Application Publication, was marked in evidence.)
MR. MONSOUR: The next document is -- the front page of it says, "Appendix F, MSDS Supportive Documentation." On the next page, you see, it is the agreement between Phillips Sumika and Boston Scientific Corporation.
Do you want to look at this? And behind it -- it's in the same exhibit, but behind it is -- I believe it's the Badylak rabbit study.
(Whereupon, Exhibit Number 21, Document titled Appendix F, MSDS Supportive Documentation with attached agreement, was marked in evidence.)
MR. MONSOUR: The next document is a document dated August 15, 1995. The top says, "Boston Scientific Corporation, Microvasive Urology Department. Subject: Sling Review Meeting Notes."
(Whereupon, Exhibit Number 22, 8/15/95 document, Sling Review Meeting Notes, was marked in evidence.)

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THE CLERK: The one he's looking at will be 21. This one will be 22, your Honor.
THE COURT: Thank you. You're handing 21 right now?
MR. MONSOUR: So 21 is the -- 21, your Honor, just for clarification purposes, is the agreement between Phillips Sumika and Boston Scientific.
The next one, your Honor, is a document entitled "Clinical Trials and Women's Health, Value/Risk/Investment."
(Whereupon, Exhibit Number 23, Document titled Clinical Trials and Women's Health, Value/Risk/Investment, was marked in evidence.)
THE CLERK: That will be 23, your Honor.
MR. MONSOUR: The next one is the Slings Cheat Sheet.
(Whereupon, Exhibit Number 24, Slings Cheat Sheet, was marked in evidence.)
THE CLERK: That will be 24, your Honor.
MR. MONSOUR: The next one is the

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Obtryx Transobturator Mid-Urethral Sling System Marketing Sheet.
(Whereupon, Exhibit Number 25, Obtryx Transobturator Mid-Urethral Sling System Marketing Sheet, was marked in evidence.)
THE CLERK: That will be 25, your Honor.
MR. MONSOUR: The next document is the Pinnacle Directions for Use, Pelvic Floor Repair Kit.
MR. ANIELAK: I think that's already in as I.
MR. MONSOUR: Oh, it is?
MR. ANIELAK: I'm sorry, the Pinnacle -- I'm sorry, I got confused, my fault.
THE COURT: So the Pinnacle DFU would be 26?
THE CLERK: Yes, your Honor.
(Whereupon, Exhibit Number 26, Pinnacle Directions for Use, was marked in evidence.)
MR. MONSOUR: And the last one I have, your Honor, is the Uphold Vaginal Support System

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DFU.
(Whereupon, Exhibit Number 27, Uphold Vaginal Support System DFU, was marked in evidence.)
THE CLERK: That will be 27, your Honor.
MR. MONSOUR: And that's all I have at this point in time, your Honor. Thank you.
MR. ANIELAK: Your Honor, those are admitted in light of the rulings of the Court?
THE COURT: All right. Subject to the prior rulings.
And your next witness?
MR. OSBORNE: Your Honor, Plaintiff would call Maya Matusovsky, who is an employee, she is from the group marketing division, or the group marketing manager of Boston Scientific. She will be called by videotaped deposition.
We have three exhibits to offer into evidence as part of her testimony. The first will be referred to in the deposition as 375, it is titled "Sling City," and it will be our next numbered exhibit. This will also be referred as 376 as well in a slightly different form, but

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we're just offering this one copy into evidence.
THE CLERK: Want that marked, your Honor?
THE COURT: Yes. All subject to the rulings made earlier.
MR. OSBORNE: Correct, your Honor.
THE CLERK: Exhibit Number 28, your Honor.
(Whereupon, Exhibit Number 28, Document titled Sling City, was marked in evidence.)
MR. OSBORNE: Plaintiffs would also offer next into evidence, which is referred to as 377 in the video, it's entitled "2008 Sling City Tournament."
THE CLERK: Exhibit Number 29, your Honor.
(Whereupon, Exhibit Number 29, Document titled 2008 Sling City Tournament, was marked in evidence.)
MR. OSBORNE: And next an e-mail from Ms. Matusovsky dated October 1, 2008. It's referred to as Exhibit 379 in the video.
THE CLERK: That will be Exhibit

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Number 30, your Honor.
THE COURT: Thank you.
(Whereupon, Exhibit Number 30, Copy of 10/1/08 e-mail, was marked in evidence.)
MR. ANIELAK: Your Honor, Boston Scientific will have one exhibit to offer during this deposition, that is Women's Health Portfolio Brochure, and that will go in as Exhibit 31.
(Whereupon, Exhibit Number 31, Women's Health Portfolio Brochure, was marked in evidence.)
THE CLERK: So marked, your Honor.
THE COURT: Is that referred to during the testimony?
MR. ANIELAK: It is, your Honor.
THE COURT: And by what number, do you know?
MR. ANIELAK: Exhibit 392, your Honor.
THE COURT: Thank you.
MR. ANIELAK: I'm sorry, 393.

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MAYA MATUSOVSKY,
appearing by videotaped deposition, testified as follows:
(Videotape played.)
(Videotape interrupted.)
MR. ANIELAK: Your Honor, can we approach?
(Sidebar.)
MR. ANIELAK: I believe that was supposed to be out. The next few questions I think are out as well.
MR. OSBORNE: I think they are as well.
THE COURT: All right. I saw you tell him to take that off. Can he skip ahead then?
MR. OSBORNE: We'll switch to 379, which is the document.
(End of sidebar.)
(Videotaped deposition continued.)
(End of videotaped testimony.)
THE COURT: Just make a note, we need to mark for identification the DVD or tape. DVD, is that what was used?
MR. OSBORNE: Yes, your Honor. We can

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do that, your Honor.
THE COURT: Thank you.
MR. OSBORNE: Yes, your Honor.
Plaintiff would call as her next witness Lee Sullivan, who is also a Boston Scientific employee, the director of sales. She is also going to be testifying by way of videotape.
We will offer three exhibits as part of her testimony.
THE COURT: If the jurors want to stand and stretch, feel free to do so.
You're going to have to wait for Mr. Lynch to do that. If you would just state what they are, and I'll assign numbers.
MR. OSBORNE: Okay. The first, your Honor, is referred to in the video as Exhibit 550. It's titled "Sales Growth and Investment, Urogyn Investment Proposal, Accelerate Pelvic Floor Growth." The date is May 28, 2008.
THE COURT: All right. That is going to be Exhibit 32.
MR. OSBORNE: Correct.

(Whereupon, Exhibit Number 32, 5/28/08 document titled Sales Growth and Investment, Urongyn Investment Proposal, Accelerate Pelvic Floor Growth, was marked in evidence.)

MR. OSBORNE: The second, your Honor, is referred to in the videotape as Exhibit 561, it's titled "Boston Scientific, February 2, 2006 General Session."

(Whereupon, Exhibit Number 33, Document titled Boston Scientific, February 2, 2006, General Session, was marked in evidence.)

THE COURT: All right. That will be 33.

MR. OSBORNE: The third document is exhibit -- is referred in the video as Exhibit 562, it is titled "Lee Sullivan, Sunday General Session Podium Script."

(Whereupon, Exhibit Number 34, Document titled Lee Sullivan, Sunday General Session Podium Script, was marked in evidence.)

THE COURT: All right. So that will be Exhibit 34.

MR. OSBORNE: Should I --

THE COURT: If would you give them to Officer Serra, he'll bring them up to me.

MR. OSBORNE: Yep.

Thank you, Judge.

LEE SULLIVAN,

appearing by videotaped deposition, testified as follows:

(Videotape played.)

(End of videotape.)

THE COURT: Does that complete that presentation?

All right. Ladies and gentlemen, it's just about 4:00 o'clock, so we'll excuse you until tomorrow morning. Have a pleasant evening, and we'll see you tomorrow at 9:00.

THE COURT OFFICER: All rise. Jury out.

THE COURT: Court will stay in session.

(Jury not present.)

THE CLERK: Please be seated. Court is now in session.

THE COURT: May I see the exhibits that went in earlier?

THE CLERK: (Handing).

THE COURT: All right. I told you originally that evidentiary rulings are preliminary and that they change during the course of the trial. When I ruled on the admissibility of the portions, I think it was of the Sling City presentation which related to going into the operating room and the like, even if the doctor says no, I was not familiar with Ms. Sullivan's testimony and the emphasis on integrity, trust, and the like. And it seems to me that the portions that were excluded from this area, that they are admissible, given what I've just heard with respect to the Sullivan testimony.

So I would assume that you would want to do that first thing tomorrow morning?

MR. MONSOUR: What we'll do is we'll just prepare a small cut. And I don't know whether they will want any counter-designations.

THE COURT: And you'll want to substitute an exhibit that includes the portions that were originally excluded.

MR. MONSOUR: Yes, a completed Sling City, your Honor. Thank you.

THE COURT: All right. Anything else? No.

So tomorrow you anticipate Ms. Rao. We've done the Lee Sullivan video.

So apart from Ms. Rao, what else do you have tomorrow?

MR. OSBORNE: Yes, your Honor. We will call the Plaintiff tomorrow. And possibly if we get that far, probably read some of Dr. Childs's deposition.

THE COURT: All right. And, again, with respect to every witness who has presented evidence via video, we do need to mark those, because they're not part of the transcript of the trial.

MR. MONSOUR: How would you like us to do that, your Honor? We've got --

THE COURT: Well, what form is it in that you're using?

MR. MONSOUR: The form, the best one we get is from Corey here where it's got the different colors, and you can read through these. I think that's the easiest way to read through it. But if you would prefer another way, we can do that as well.

THE COURT: I just want the record to have either the videotape of the testimony -- well, I want the record to have both the videotape of the testimony as well as the transcript of the testimony that was admitted in evidence.

MR. MONSOUR: Okay.

MR. ANIELAK: We would suggest either burning a CV or providing a thumb drive.

THE COURT: Right. I'd say a CD is better.

MR. MONSOUR: So we'll do a CD and a written transcript that has our cuts and their cuts.

THE COURT: Correct.

MR. MONSOUR: Thank you.

And for Matusovsky, we'll do the first one, and then we'll do a second supplemental

one.

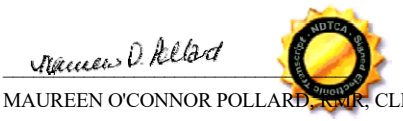
THE COURT: All right. Yes. Court will be in recess.

THE CLERK: All rise. Court will stand in recess.

(Whereupon, the proceeding were adjourned at 3:59 p.m.)

C E R T I F I C A T E

I, MAUREEN O'CONNOR POLLARD, RMR, CLR, do hereby certify that the foregoing transcript is a true and accurate transcription of my stenographic notes taken on August 18th, 2014.



MAUREEN O'CONNOR POLLARD, RMR, CLR
Realtime Systems Administrator
CSR #149108

EXHIBIT BB

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA

CHARLESTON DIVISION

IN RE: ETHICON INC.
PELVIC REPAIR SYSTEMS
PRODUCT LIABILITY LITIGATION MDL No. 2327

THIS DOCUMENT RELATES TO:

Cases Identified in the Exhibit
Attached Hereto

MEMORANDUM OPINION AND ORDER
(*Daubert* Motion re: Scott A. Guelcher, Ph.D.)

Pending before the court is the Motion to Exclude the Opinions and Testimony of Scott A. Guelcher, Ph.D. [ECF No. 1977] filed by Johnson & Johnson and Ethicon, Inc. (collectively "Ethicon"). The Motion is now ripe for consideration because briefing is complete.

I. Background

This case resides in one of seven MDLs assigned to me by the Judicial Panel on Multidistrict Litigation concerning the use of transvaginal surgical mesh to treat pelvic organ prolapse ("POP") and stress urinary incontinence ("SUI"). In the seven MDLs, there are more than 75,000 cases currently pending, approximately 30,000 of which are in this MDL.

In this MDL, the court's tasks include "resolv[ing] pretrial issues in a timely and expeditious manner" and "resolv[ing] important evidentiary disputes." Barbara J. Rothstein & Catherine R. Borden, Fed. Judicial Ctr., *Managing Multidistrict*

Litigation in Products Liability Cases 3 (2011). To handle motions to exclude or to limit expert testimony pursuant to *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), the court developed a specific procedure. In Pretrial Order ("PTO") No. 217, the court instructed the parties to file only one *Daubert* motion per challenged expert, to file each motion in the main MDL—as opposed to the individual member cases—and to identify which cases would be affected by the motion. PTO No. 217, at 4.[1]

II. Preliminary Matters

Before plunging into the heart of the Motion, a few preliminary matters need to be addressed.

I am compelled to comment on the parties' misuse of my previous *Daubert* rulings on several of the experts offered in this case. *See generally Sanchez v. Bos. Sci. Corp.*, No. 2:12-cv-05762, 2014 WL 4851989 (S.D. W. Va. Sept. 29, 2014); *Tyree v. Bos. Sci. Corp.*, 54 F. Supp. 3d 501 (S.D. W. Va. 2014); *Eghnayem v. Bos. Sci. Corp.*, 57 F. Supp. 3d 658 (S.D. W. Va. 2014). The parties have, for the most part, structured their *Daubert* arguments as a response to these prior rulings, rather than an autonomous challenge to or defense of expert testimony based on its reliability and relevance. In other words, the parties have comparatively examined expert testimony and have largely overlooked *Daubert*'s core considerations for assessing expert

[1] Ethicon identified the Wave 1 cases affected by this Motion in its attached Exhibit A [ECF No. 1977-1], which the court has attached to this Memorandum Opinion and Order. At the time of transfer or remand, the parties will be required to designate relevant pleadings from MDL 2327, including the motion, supporting memorandum, response, reply, and exhibits referenced herein.

testimony. Although I recognize the tendency of my prior evidentiary determinations to influence subsequent motions practice, counsels' expectations that I align with these previous rulings when faced with a different record are misplaced, especially when an expert has issued new reports and given additional deposition testimony.

Mindful of my role as gatekeeper for the admission of expert testimony, as well as my duty to "respect[ ] the individuality" of each MDL case, *see In re Phenylpropanolamine Prods. Liab. Litig.*, 460 F.3d 1217, 1231 (9th Cir. 2006), I refuse to credit *Daubert* arguments that simply react to the court's rulings in *Sanchez* and its progeny. Indeed, I feel bound by these earlier cases only to the extent that the expert testimony and *Daubert* objections presented to the court then are identical to those presented now. Otherwise, I assess the parties' *Daubert* arguments anew. That is, in light of the particular expert testimony and objections currently before me, I assess "whether the reasoning or methodology underlying the testimony is scientifically valid" and "whether that reasoning or methodology properly can be applied to the facts in issue." *Daubert*, 509 U.S. at 592–93. Any departure from *Sanchez*, *Eghnayem*, or *Tyree* does not constitute a "reversal" of these decisions and is instead the expected result of the parties' submission of updated expert reports and new objections to the expert testimony contained therein.

Finally, I have attempted to resolve all possible disputes before transfer or remand, including those related to the admissibility of expert testimony pursuant to *Daubert*. Nevertheless, in some instances I face *Daubert* challenges where my interest in accuracy counsels reserving ruling until the reliability of the expert

testimony may be evaluated at trial. At trial, the expert testimony will be tested by precise questions asked and answered. The alternative of live *Daubert* hearings is impossible before transfer or remand because of the numerosity of such motions in these seven related MDLs. As these MDLs have grown and the expert testimony has multiplied, I have become convinced that the critical gatekeeping function permitting or denying expert testimony on decisive issues in these cases is best made with a live expert on the witness stand subject to vigorous examination.

In the course of examining a multitude of these very similar cases involving the same fields of expertise, I have faced irreconcilably divergent expert testimony offered by witnesses with impeccable credentials, suggesting, to me, an unreasonable risk of unreliability. The danger—and to my jaded eye, the near certainty—of the admission of "junk science" looms large in this mass litigation.

The parties regularly present out-of-context statements, after-the-fact rationalizations of expert testimony, and incomplete deposition transcripts. This, combined with the above-described practice of recycling expert testimony, objections, and the court's prior rulings, creates the perfect storm of obfuscation. Where further clarity is necessary, I believe it can only be achieved through live witness testimony—not briefing—and I will therefore reserve ruling until the expert testimony can be evaluated firsthand.

III. Legal Standard

By now, the parties should be intimately familiar with Rule 702 of the Federal Rules of Evidence and *Daubert*, so the court will not linger for long on these

standards.

Expert testimony is admissible if the expert is qualified and if his or her expert testimony is reliable and relevant. Fed. R. Evid. 702; *see also Daubert*, 509 U.S. at 597. An expert may be qualified to offer expert testimony based on his or her "knowledge, skill, experience, training, or education." Fed. R. Evid. 702. Reliability may turn on the consideration of several factors:

> (1) whether a theory or technique can be or has been tested; (2) whether it has been subjected to peer review and publication; (3) whether a technique has a high known or potential rate of error and whether there are standards controlling its operation; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Cooper v. Smith & Nephew, Inc., 259 F.3d 194, 199 (4th Cir. 2001) (citing *Daubert*, 509 U.S. at 592–94). But these factors are neither necessary to nor determinative of reliability in all cases; the inquiry is flexible and puts "principles and methodology" above conclusions and outcomes. *Daubert*, 509 U.S. at 595; *see also Kumho Tire Co. v. Carmichael*, 525 U.S. 137, 141, 150 (1999). Finally, and simply, relevance turns on whether the expert testimony relates to any issues in the case. *See, e.g.*, *Daubert*, 509 U.S. at 591–92 (discussing relevance and helpfulness).

At bottom, the court has broad discretion to determine whether expert testimony should be admitted or excluded. *Cooper*, 259 F.3d at 200.

IV. Discussion

Dr. Guelcher is a chemical engineer who has over twenty years of experience in his field. Ethicon challenges his testimony on several grounds.

a. Complications

Ethicon argues that Dr. Guelcher is unqualified to offer his complications opinions, and that the opinions are otherwise unreliable. Dr. Guelcher is not a medical doctor; instead, he is a chemical engineer. Dr. Guelcher has not examined patients, and he has not conducted differential diagnoses. Dr. Guelcher is simply not qualified to offer opinions on medical complications that may be caused by polymer degradation. Accordingly, Dr. Guelcher's opinions regarding complications resulting from alleged polypropylene degradation are **EXCLUDED**.

b. Mesh Properties

Ethicon asks the court to exclude Dr. Guelcher's degradation testimony, challenging it as unreliable on multiple fronts.

First, Ethicon argues that Dr. Guelcher's opinions should be excluded because he has chosen not to rely on his own testing regarding oxidative degradation. In response, the plaintiffs explain that Dr. Guelcher's study has not yet been published, has not been subject to peer review, and is otherwise unfinished. Interestingly, Ethicon argues that Dr. Guelcher should be required to testify regarding his study, while simultaneously pointing out that this court has already ruled testimony about the study is unreliable. *See, e.g.*, *Winebarger v. Bos. Sci. Corp.*, No. 2:13-cv-28892, 2015 WL 1887222, at *25 (S.D. W. Va. Apr. 24, 2015). This argument is without merit. I will not exclude Dr. Guelcher's opinions merely because he chooses not to rely on his own incomplete studies. Ethicon's Motion on this issue is **DENIED**.

Second, Ethicon argues that Dr. Guelcher's degradation opinions should be

excluded because not all of the scientific literature upon which he relied examined Prolene specifically, but examined polypropylene generally. I disagree that the supposed distinction between Ethicon's Prolene and generic polypropylene renders studies on the latter unhelpful when discussing Prolene. *See, e.g.*, *Huskey v. Ethicon, Inc.*, 29 F. Supp. 3d 691, 703 (S.D. W. Va. 2014) (rejecting Ethicon's argument as "wholly conceived by lawyers, unfounded in science"). Insofar as Ethicon seeks exclusion of Dr. Guelcher's opinions because he does not account for the differences between polypropylene and Prolene, its Motion is **DENIED**.

Third, Ethicon argues that Dr. Guelcher's opinions are unreliable because they are based in part on unpublished Ethicon studies—a Prolene suture study and a "seven-year dog study" of Prolene sutures—that allegedly do not support his opinion. Mem. 14 [ECF No. 1981]. Ethicon does not contest, however that its internal documents report evidence of polypropylene oxidation and degradation; instead, Ethicon challenges the conclusions of those reports by suggesting that degradation should be measured by methods different than those used in the studies. Such concerns are better suited for cross-examination. Moreover, I have previously ruled that an expert may testify as to a review of internal corporate documents for the purpose of explaining the basis of his expert opinions, as Dr. Guelcher does here. *Huskey*, 29 F. Supp. 3d at 702–03. I do not find that Dr. Guelcher's partial reliance on Ethicon's internal documents relating to degradation renders his opinions unreliable. Nor am I persuaded that evidence of these studies demonstrating the degradation of Prolene sutures will be prejudicial unless Ethicon can introduce

evidence that the sutures received FDA approval. Ethicon's Motion is **DENIED** on these points.

V. Recurring Issues

Many of the *Daubert* motions filed in this MDL raise the same or similar objections.

One particular issue has been a staple in this litigation, so I find it best to discuss it in connection with every expert. A number of the *Daubert* motions seek to exclude FDA testimony and other regulatory or industry standards testimony. To the extent this Motion raises these issues it is **GRANTED in part** and **RESERVED in part** as described below.

I have repeatedly excluded evidence regarding the FDA's section 510(k) clearance process in these MDLs, and will continue to do so in these cases, a position that has been affirmed by the Fourth Circuit. *In re C. R. Bard, Inc.*, 81 F.3d 913, 921–23 (4th Cir. 2016) (upholding the determination that the probative value of evidence related to section 510(k) was substantially outweighed by its possible prejudicial impact under Rule 403). Because the section 510(k) clearance process does not speak directly to safety and efficacy, it is of negligible probative value. *See In re C. R. Bard*, 81 F.3d at 920 ("[T]he clear weight of persuasive and controlling authority favors a finding that the 510(k) procedure is of little or no evidentiary value."). Delving into complex and lengthy testimony about regulatory compliance could inflate the perceived importance of compliance and lead jurors "to erroneously conclude that regulatory compliance proved safety." *Id.* at 922. Accordingly, expert

testimony related to the section 510(k) process, including subsequent enforcement actions and discussion of the information Ethicon did or did not submit in its section 510(k) application, is **EXCLUDED**. For the same reasons, opinions about Ethicon's compliance with or violation of the FDA's labeling and adverse event reporting regulations are **EXCLUDED**. In addition to representing inappropriate legal conclusions, such testimony is not helpful to the jury in determining the facts at issue in these cases and runs the risk of misleading the jury and confusing the issues. Insofar as this Motion challenges the FDA-related testimony discussed here, the Motion is **GRANTED**.

A number of experts also seek to opine on Ethicon's compliance with design control and risk management standards. Some of this testimony involves the FDA's quality systems regulations, and some—likely in an attempt to sidestep my anticipated prohibition on FDA testimony—involve foreign regulations and international standards. I find all of this proposed testimony of dubious relevance. Although these standards relate to how a manufacturer should structure and document risk assessment, the standards do not appear to mandate any particular design feature or prescribe the actual balance that must be struck in weighing a product's risk and utility. Nor is it clear that the European and other international standards discussed had any bearing on the U.S. medical device industry when the device in question was being designed.

Nevertheless, because the nuances of products liability law vary by state, I will refrain from issuing a blanket exclusion on design process and control standards

testimony, whether rooted in the FDA or otherwise. Each standard must be assessed for its applicability to the safety questions at issue in this litigation, consistent with state law. I am without sufficient information to make these findings at this time. Accordingly, I **RESERVE** ruling on such matters until a hearing, where the trial judge will have additional context to carefully evaluate the relevance and potential prejudicial impact of specific testimony.

Similarly, I doubt the relevance of testimony on the adequacy of Ethicon's clinical testing and research, physician outreach, or particular product development procedures and assessments otherwise not encompassed by the above discussion. Again, such matters seem to say very little about the state of the product itself (i.e., whether or not it was defective) when it went on the market. But because the scope of relevant testimony may vary according to differences in state products liability law, I **RESERVE** ruling on such matters until they may be evaluated in proper context at a hearing before the trial court before or at trial.

Additional—and more broad—matters also warrant mention. While some of these concerns may not apply to this particular expert, these concerns are raised so frequently that they are worth discussing here.

First, many of the motions seek to exclude state-of-mind and legal-conclusion expert testimony. Throughout these MDLs, the court has prohibited the parties from using experts to usurp the jury's fact-finding function by allowing testimony of this type, and I do the same here. *E.g.*, *In re C. R. Bard, Inc.*, 948 F. Supp. 2d 589, 611 (S.D. W. Va. 2013); *see also, e.g.*, *United States v. McIver*, 470 F.3d 550, 562 (4th Cir.

2006) ("[O]pinion testimony that states a legal standard or draws a legal conclusion by applying law to the facts is generally inadmissible."); *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 546 (S.D.N.Y. 2004) ("Inferences about the intent and motive of parties or others lie outside the bounds of expert testimony."). Additionally, an expert may not offer expert testimony using "legal terms of art," such as "defective," "unreasonably dangerous," or "proximate cause." *See Perez v. Townsend Eng'g Co.*, 562 F. Supp. 2d 647, 652 (M.D. Pa. 2008).

Second, and on a related note, many of the motions seek to prohibit an expert from parroting facts found in corporate documents and the like. I caution the parties against introducing corporate evidence through expert witnesses. Although an expert may testify about his or her review of internal corporate documents solely for the purpose of explaining the basis for his or her expert opinions—assuming the expert opinions are otherwise admissible—he or she may not offer testimony that is solely a conduit for corporate information.

Third, many of the motions also ask the court to require an expert to offer testimony consistent with that expert's deposition or report or the like. The court will not force an expert to testify one way or another. To the extent an expert offers inconsistent testimony, the matter is more appropriately handled via cross-examination or impeachment as appropriate and as provided by the Federal Rules of Evidence.

Fourth, in these *Daubert* motions, the parties have addressed tertiary evidentiary matters like whether certain statements should be excluded as hearsay.

The court will not exclude an expert simply because a statement he or she discussed may constitute hearsay. *Cf. Daubert*, 509 U.S. at 595. Hearsay objections are more appropriately raised at trial.

Finally, in some of the *Daubert* motions, without identifying the specific expert testimony to be excluded, the parties ask the court to prevent experts from offering testimony the expert is not qualified to offer. I will not make speculative or advisory rulings. I decline to exclude testimony where the party seeking exclusion does not provide specific content or context.

VI. Conclusion

The court **DENIES in part**, **GRANTS in part**, and **RESERVES in part** the Motion to Exclude the Opinions and Testimony of Scott A. Guelcher, Ph.D. [ECF No. 1977].

The court **DIRECTS** the Clerk to file a copy of this Memorandum Opinion and Order in 2:12-md-2327 and in the Ethicon Wave 1 cases identified in the Exhibit attached hereto.

ENTER: August 31, 2016

JOSEPH R. GOODWIN
UNITED STATES DISTRICT JUDGE

AMENDED EXHIBIT A

Guelcher

Case Name	Case Number
Babcock, Marty	2:12cv01052
Barker, Daphne & Gary	2:12cv00899
Baugher, Dorothy	2:12cv01053
Beach, Harriet	2:12cv00476
Byrd, Myra & Richard	2:12cv00748
Collins, Fran Denise	2:12cv00931
Daino, Constance & Anthony	2:12cv01145
Dixon, Dennis W., re estate of Virginia M. Dixon, dec'd	2:12cv01081
Durham, Lois & Gerald	2:12cv00760
Forester, Karen & Joel	2:12cv00486
Freeman, Shirley & William	2:12cv00490
Freitas, Monica & Kenneth	2:12cv01146
Guinn, Susan	2:12cv01121
Hagans, Wendy	2:12cv00783
Harter, Beth ~~& Stuart~~	2:12cv00737
Herrera-Nevarez, Rocio	2:12cv01294
Holmes, Jeanie	2:12cv01206
Holzerland, Mary & Darin	2:12cv00875
Hoy, Lois & Robert	2:12cv00876
Johnson, Myndal	2:12cv00498
Jones, Holly & Jason	2:12cv00443
Joplin, ~~Deborah Lynn~~ Debra Lynn	2:12cv00787
Kirkpat~~r~~ick, Margaret	2:12cv00746
Kivel, Beverly	2:12cv00591
Lankston, Cheryl	2:12cv00755
Long, Heather	2:12cv01275
Massey, Donna & Charles	2:12cv00~~347~~ 880
Morrison, Angela & Bradley	2:12cv00800
Quijano, Maria Eugenia	2:12cv00799
Rhynehart, Penny	2:12cv01119
Sacchetti, Denise	2:12cv01148
Schnering, Debra A. & Donald, Sr.	2:12cv01071
Scholl, Sheri ~~& Gary~~	2:12cv00738
Shepherd, Donna	2:12cv00967
Smith, Cindy	2:12cv01149
Springer, Cherise & Marty	2:12cv00997
Stubblefield, Margaret	2:12cv00842
Thompson, Lisa & Roger	2:12cv01199
Thurston, Mary ~~& Kenneth~~	2:12cv00505
Walker, Shirley & Roosevelt	2:12cv00873

Case Name	Case Number
Warlick, Cathy	2:12cv00276
Waynick, Laura ~~& David~~	2:12cv01151
Wheeler, Rebecca & David	2:12cv01088
Williams, Nancy	2:12cv00511
Wiltgen, Christine & Mark S.	2:12cv01216
Wright, Thelma	2:12cv01090

EXHIBIT CC

Histologic Comparison of Pubovaginal Sling Graft Materials: A Comparative Study

Anthony J. Woodruff, Emily E. Cole, Roger R. Dmochowski, Harriette M. Scarpero, Edwin N. Beckman, and J. Christian Winters

OBJECTIVES Little is known about the host response to the various biologic and synthetic graft materials used as substitutes for autologous fascia. We investigated the host response to sling graft materials in humans.

METHODS A total of 24 women undergoing sling revision had a portion of the graft material removed for comparative analysis. At exploration, the degree of graft preservation (integrity), encapsulation, infection, and fibrosis was quantified. A histopathologic analysis was performed by systematically examining each specimen for the inflammatory response, neovascularity, and host fibroblast infiltration.

RESULTS A total of 24 grafts were explanted at 2-34 months after implantation. The indications for removal were a lack of sling efficacy in 2, urinary retention in 9, and sling obstruction in 13. The types of graft material were polypropylene mesh (PPM) in 10, autologous fascia in 5, porcine dermis in 4, cadaveric dermis in 3, and cadaveric fascia in 2. No graft degradation had occurred in PPM material. Autologous and cadaveric fascia had the most demonstrable graft degradation. No encapsulation had occurred with autologous fascia or PPM. The porcine dermis was the most encapsulated. No host infiltration had occurred with the encapsulated porcine grafts, and only peripheral infiltration of fibroblasts had occurred in the cadaveric grafts. The PPM grafts had the greatest number of fibroblasts throughout the entire graft. Neovascularity was the most prevalent in mesh and was also present in the autologous fascia. Giant cells were seen in two mesh and two porcine grafts.

CONCLUSIONS The results of our study have shown that porcine dermis has the potential to encapsulate. The degree of host tissue infiltration was greatest with PPM, and no degradation of the mesh material had occurred with time. UROLOGY 72: 85–89, 2008. © 2008 Elsevier Inc.

Stress urinary incontinence is a very bothersome condition that affects 10%-20% of the female population.[1] The surgical treatment of stress urinary incontinence has evolved during the past several decades from retropubic and transvaginal urethral suspension procedures to the primary use of sling procedures. The American Urologic Association Stress Urinary Guidelines Panel determined that pubovaginal slings and retropubic suspensions were most efficacious in the treatment of stress urinary incontinence.[2] Chakin et al.[3] demonstrated the successful use of a pubovaginal sling in women presenting with all types of stress urinary incontinence. Subsequently, pubovaginal sling procedures became accepted as the reference standard in the surgical management of stress urinary incontinence, and several investigators have reported the long-term efficacy and safety of the procedure.[4–6] To minimize the morbidity of graft harvest, biologic and synthetic graft materials have been increasingly used in sling surgery. Decreased perioperative pain and hospital stay have been associated with the use of graft substitutes.[7] Despite the encouraging early results, some data have suggested greater intermediate and late failure after biologic sling procedures.[8,9] Synthetic slings, although associated with excellent early results, have been reported to be sources of infection and occasional urethral erosion.[10]

With the emerging use of graft substitution materials, an increased knowledge of the host response to these materials is needed. Insufficient data are available to assess the host response to these materials after implantation. These data can have a variety of implications regarding efficacy and safety. Therefore, we sought to compare the histopathologic characteristics of these various sling materials after explantation during sling revision surgery. Perhaps by comparing the changes in the host–graft relationships of these various materials, we might be better able to understand the

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potential clinical significance of using histologic data to guide synthetic sling grafts.

MATERIAL AND METHODS

A total of 24 consecutive women undergoing sling revision surgery had portions of their slings removed at explantation for the following indications: lack of efficacy in 2, urinary retention in 9, and sling obstruction in 13. The patients were classified as obstructed if they had persistent lower urinary tract symptoms and had a clinical diagnosis of obstruction as a result of the sling procedure. Patients in retention were those reliant on intermittent catheterization, which became necessary after the sling procedure. These graft explantations occurred at two sites: Vanderbilt Medical Center and the Ochsner Clinic Foundation. During exploration, each graft was examined and graded systematically by the explanting surgeon. Each graft was inspected for signs of encapsulation, infection, fibrosis, and degree of preservation (integrity). Encapsulation was defined as a fibrous rim of tissue surrounding and isolating the graft material. Encapsulation was quantified from no encapsulation, which consisted of the graft within the host tissues, to severe encapsulation, consisting of a thick capsule completely isolating the graft material. Infection was defined as gross evidence of purulence or cellulitis consistent with a clinical infection. Degradation was defined as a loss of graft structure, ranging from no degradation, which is characterized by no loss of graft thickness or structure to severe degradation, in which thinning of the graft and breakdown of the graft structure had occurred, disrupting the scaffold of support.

After gross examination, these samples were placed in formalin solution and underwent conventional hematoxylin-eosin staining procedures. Similar sectioning techniques were used for the various material types. Each specimen was then systematically examined microscopically by a pathologist (E.N.B.) who was unaware of the material type. The pathologist specifically inspected each graft to quantify neovascularity, inflammatory response, host fibroblast infiltration, and areas of necrosis. Neovascularity was defined as the presence of blood vessels within the graft. Blood vessels were defined as endothelial-lined vessels containing erythrocytes. Inflammation was identified by the quantification of white blood cells, macrophages, or foreign body reaction (eg, giant cells). Host cellular infiltration was identified by the quantification of fibroblasts within the graft material.

The patient records were reviewed for any host factors that could potentially inhibit graft remodeling. These factors included age older than 70 years, diabetes, steroid use, smoking history, and a history of graft infection/complications. All variables were analyzed systematically by comparing each graft material. Additional analyses of the gross and histopathologic characteristics of the graft materials were compared according to the interval from surgery at which the material was extracted.

RESULTS

A total of 24 grafts were explanted 2-65 months after implantation. The types of materials explanted included polypropylene mesh (PPM) in 10, cadaveric fascia in 2, cadaveric dermis in 3, porcine dermis in 4, and autologous fascia in 5. The average age of the patients who underwent explanation was 60.3 years for those with PPM, 58.6 years for those with cadaveric dermis, 62.8 years for those autologous fascia, and 60 years for those with porcine dermis. A trend was noted for advanced age in the porcine dermis group, reflective of selection bias. No patient had been taking steroids chronically, and none had had a history of graft infection or rejection before the study. Tobacco use was present in 30% of PPM, 0% of autologous fascia, 20% of cadaveric dermis, and 50% of porcine dermis patients. The porcine dermis patients had a greater frequency of tobacco use.

On gross inspection, the autologous fascia grafts demonstrated only moderate degradation; however, the integrity of the grafts appeared intact, with no compromise of the graft scaffolding. The autologous material displayed no evidence of encapsulation or gross infection. Microscopically, the autologous fascia showed moderate and uniform infiltration of host fibroblasts, as well as neovascularization. No evidence of foreign body reaction was evident, with no inflammatory cell infiltrate.

The porcine dermis grafts were grossly free of degradation or thinning and displayed an appearance very similar to that at implantation. Each was severely encapsulated and completely separate from the periurethral tissue. As might be expected from their gross appearance, these grafts microscopically appeared completely acellular without any evidence or neovascularization or host infiltration.

The cadaveric tissues demonstrated the most degradation of all harvested materials, as well as mild to moderate encapsulation. The microscopic specimens demonstrated host infiltration of fibroblasts only at the periphery of the grafts, with the central portion of all but one specimen remaining acellular. All grafts were free of neovascularization.

The PPM explants displayed no evidence of degradation or encapsulation and had the greatest degree of host tissue infiltration. Microscopically, host infiltration was abundant and displayed throughout each graft. These grafts demonstrated the greatest degree of neovascularity. A foreign body reaction was also evident by the presence of giant cells, macrophages, and occasional calcification. A summary of the comparison of graft materials is included in Table 1 and Figures 1 and 2.

When the grafts were analyzed according to the interval after surgery, similar changes were noted. Over time, the degradation appeared progressive in the patients with cadaveric grafts. This appearance was fairly consistent throughout all intervals, with the exception of one cadaveric fascia graft that had the presence of fibroblast infiltration throughout the entire graft 38 months after it had been implanted. Despite this, we were able to localize all sling grafts in this group of patients. Other graft materials did not demonstrate this trend of progressive degradation with time.

COMMENT

As pubovaginal slings gained widespread acceptance in the surgical management of stress urinary incontinence, the use of grafts as a substitute for autologous fascia has

Table. Gross and histopathologic comparison of graft materials

Graft material	Patients (n)	Graft Degradation	Encapsulation	Infection	Host Fibroblasts (Location)	Neovascularity
PPM	10	None	None	None	Many (uniform)	Moderate
Cadaveric fascia	2	Moderate	None	None	Few (peripheral)	None
Cadaveric dermis	3	Mild	Mild	None	Few (peripheral)	None
Porcine dermis	4	None	Severe	None	None	None
Autologous fascia	5	Moderate	None	None	Moderate (peripheral)	Few

PPM = polypropylene mesh.

Figure 1. Variance of gross appearance of graft material at explanation: (**A**) significant infiltration of host tissue in polypropylene mesh, (**B**) lack of host infiltration in porcine dermis.

become commonplace. First introduced by Jarvis and Fowlie,[11] using porcine dermis, these investigators reported cases of "vaginal weeping." The practice became widely accepted after Handa et al.[12] described using cadaveric fascia lata, which was readily available from many tissue banks. Initially, the results using these materials were encouraging. However, several subsequent reports[9,10,13] of intermediate and late sling failures with these materials led to concerns regarding the use of biologic grafts as sling substitutes. The use of PPM offers an attractive advantage, but concerns regarding infection, foreign body reaction, and erosion exist. Few data are available regarding the biocompatibility of these materials—particularly after transvaginal implantation. The industry standard of biocompatibility testing requires subcutaneous placement of materials. Does this translate to biocompatibility after transvaginal implantation? As we continue to debate the ideal graft to substitute for autologous fascia, we must have a better understanding of their biocompatibility and acceptance by the host with time.

To better understand the graft–host relationship, we systematically examined the histopathologic characteristics of various graft materials after they were explanted from human subjects undergoing sling revision surgery. Using similar tissue processing and staining techniques, these samples were examined systematically and compared with each other. Our examination revealed significant differences in the gross and microscopic findings in the various materials. Autologous fascia had the greatest degree of host fibroblast infiltration with minimal inflammatory or foreign body reaction. This material was consistently intact, with a small amount of sling degradation at explantation. In contrast, the cadaveric dermis and fascia had little host fibroblast infiltration and little neovascularity, particularly within the central aspects of the graft. In addition, inconsistencies were found with this material grossly, with most specimens exhibiting significant thinning and degradation of the graft, disrupting the sling scaffold. Synthetic materials actually demonstrated the greatest amount of fibroblast ingrowth and tissue ingrowth into the specimen. Grossly, the mesh lattice was completely incorporated with viable host tissue. No degradation or disruption of the graft was found, and the substance of the graft was completely infiltrated by host tissue. Microscopically, the synthetic material had large amounts of fibroblasts and also exhibited a foreign body reaction characterized by giant cells and occasional calcification. Although the foreign body reaction was visible microscopically, no gross evidence was found of graft disruption or adverse effects on the host because of this foreign body reaction. Finally, the porcine dermis materials had the greatest propensity to encapsulate. The porcine dermis had a rind around it, which isolated the graft from the periurethral tissue. In addition to this, no host fibroblast infiltration, no inflammatory reaction, and no foreign body reaction was found. This was presumably because this material was walled off, with no access of the host to the material. The substrate of the graft was intact; in fact, the graft appeared similar to its original appearance at implantation.

Although this study did not correlate clinical outcomes, perhaps the histologic findings reflect some of the present controversy. The intermediate failures of slings using cadaveric materials have been previously described,[14] with the material being thinned or absent. As

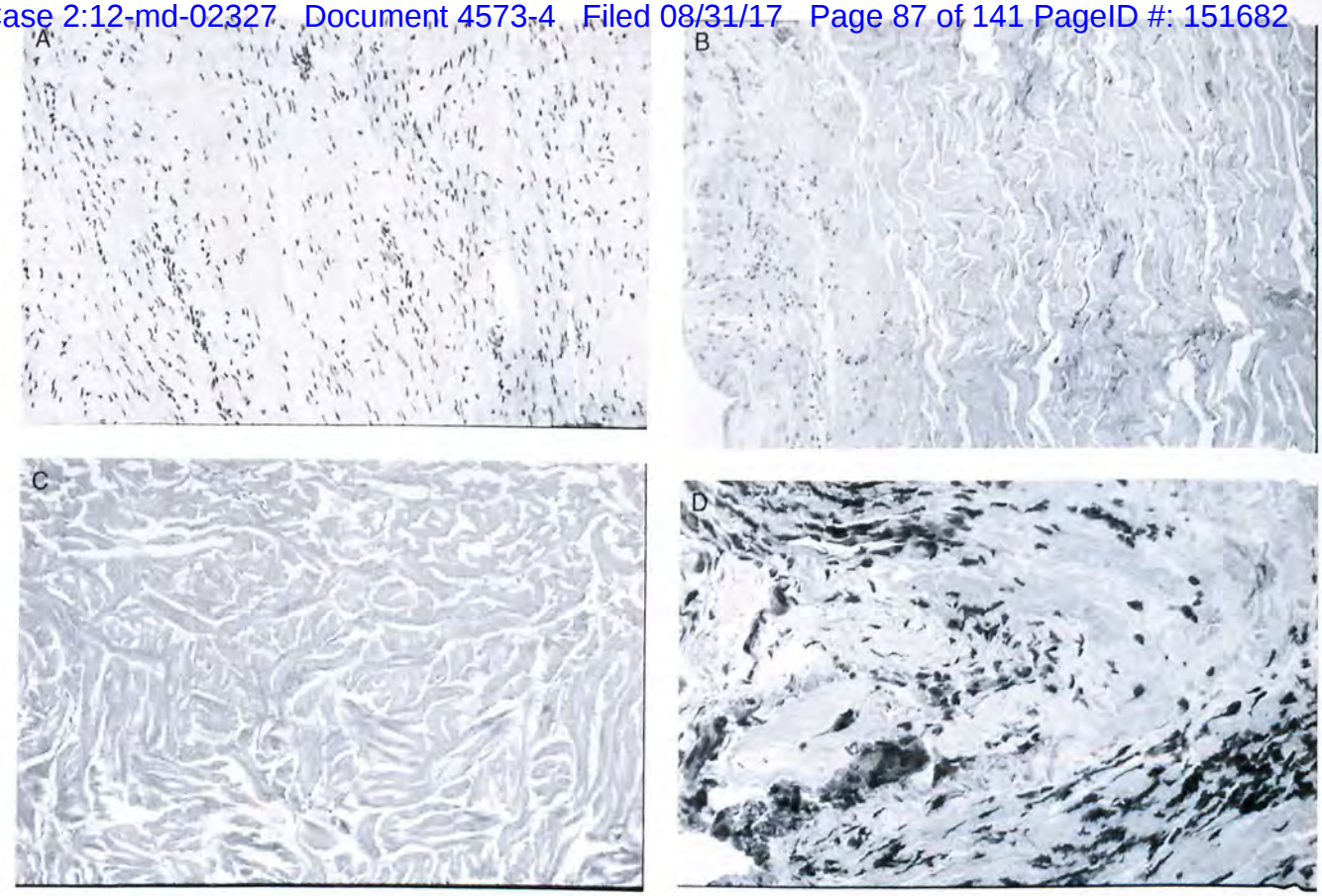

Figure 2. Variance of microscopic appearance of graft materials: (**A**) autologous fascia, (**B**) cadaveric fascia, (**C**) porcine dermis, (**D**) polypropylene mesh.

in our study, the degradation of these materials has been reported. The porcine dermis grafts also had a propensity to encapsulate, as previously reported in various studies.[15] This could ultimately affect the long-term viability of this graft material and also create potential complications such as pain and/or urinary retention.[16] However, the implications of encapsulation are largely unproved. Our data suggest that the tissue ingrowth in synthetic material is significant. Degradation of this material was not seen, particularly compared with that present in the cadaveric materials in this study. This implies that the synthetic materials are durable. To date, no significant data have demonstrated intermediate failures with these procedures.

The limitations of this study were significant. First, our study lacked standardization of the histopathologic findings regarding host remodeling. No uniform grading system is available that can be used to compare these various materials. This is clearly needed to facilitate an accurate comparison of studies of the histologic features of these materials. Second, the graft materials were not explanted at definitive points after implantation. Such a study is unlikely to be performed in human models because this would require removing grafts in women without symptoms. However, this could have affected the variance in the remodeling of our specimens.

Despite these limitations, we believe these data have clearly demonstrated that the human body reacts to these various sling materials differently. The host ingrowth in synthetic material was significantly greater compared with that with biologic materials. The clinical implications are unknown, but our results clearly indicate that additional investigation into host tissue remodeling is warranted. An animal model that replicates transvaginal insertion is needed to facilitate controlled comparisons. Additionally, consensus is needed on how to examine these materials after they are explanted from human subjects to gain a better understanding of the host response to these tissues.

CONCLUSIONS

The results of our study have demonstrated that porcine dermis has a propensity to encapsulate, which we assert could retard host infiltration into the graft. The degree of host infiltration was greatest in PPM. Considerable research is needed to understand the human host response to the various graft materials used for pubovaginal sling surgery.

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EXHIBIT DD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence

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ABSTRACT

BACKGROUND

Many surgical procedures are available for women with urinary stress incontinence, yet few randomized clinical trials have been conducted to provide a basis for treatment recommendations.

METHODS

We performed a multicenter, randomized clinical trial comparing two procedures — the pubovaginal sling, using autologous rectus fascia, and the Burch colposuspension — among women with stress incontinence. Women were eligible for the study if they had predominant symptoms associated with the condition, a positive stress test, and urethral hypermobility. The primary outcomes were success in terms of overall urinary-incontinence measures, which required a negative pad test, no urinary incontinence (as recorded in a 3-day diary), a negative cough and Valsalva stress test, no self-reported symptoms, and no retreatment for the condition, and success in terms of measures of stress incontinence specifically, which required only the latter three criteria. We also assessed postoperative urge incontinence, voiding dysfunction, and adverse events.

RESULTS

A total of 655 women were randomly assigned to study groups: 326 to undergo the sling procedure and 329 to undergo the Burch procedure; 520 women (79%) completed the outcome assessment. At 24 months, success rates were higher for women who underwent the sling procedure than for those who underwent the Burch procedure, for both the overall category of success (47% vs. 38%, $P=0.01$) and the category specific to stress incontinence (66% vs. 49%, $P<0.001$). However, more women who underwent the sling procedure had urinary tract infections, difficulty voiding, and postoperative urge incontinence.

CONCLUSIONS

The autologous fascial sling results in a higher rate of successful treatment of stress incontinence but also greater morbidity than the Burch colposuspension. (ClinicalTrials.gov number, NCT00064662.)

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Urinary incontinence affects an estimated 15 to 50% of women,[1,2] resulting in a significant medical, social, and economic burden.[1] In 1995 dollars, the annual direct costs of incontinence in the United States were estimated to be more than $16 billion.[3] Among women with incontinence, 50 to 80% are identified as having stress incontinence,[4] or involuntary leakage of urine resulting from physical exertion or sneezing and coughing.[5] Although the initial treatment of stress incontinence is often nonsurgical (behavioral therapy, pelvic-floor exercises, or incontinence devices), surgical treatment is considered for patients who are bothered by persistent symptoms. An estimated 4 to 10% of women in the United States undergo surgery intended to restore continence,[6] and this rate has increased steadily during the past 20 years.[7,8]

Many surgical procedures have been described for women with stress incontinence, yet few randomized clinical trials have been conducted to provide a basis for treatment recommendations. The fascial-sling procedure and Burch colposuspension are two well-established procedures with reported cure rates of 70 to 85% at 5 to 8 years.[9,10] In the Burch modified colposuspension,[11] the anterior vaginal wall is suspended (at the level of the bladder neck) with permanent sutures tied to the iliopectineal ligament (Fig. 1A). In the autologous sling procedure,[12] a harvested strip of rectus fascia is placed transvaginally at the level of the proximal urethra. The fascial strip is secured superiorly to the rectus fascia with permanent sutures (Fig. 1B). Although it has been suggested that the sling procedure may result in higher cure rates, this advantage may be offset by increased obstructive complications, such as voiding dysfunction and urge incontinence.[13,14] We conducted a multicenter, randomized surgical trial, the Stress Incontinence Surgical Treatment Efficacy Trial, to compare the efficacy and safety of the sling and Burch procedures 24 months after surgery.

METHODS

PATIENTS AND STUDY DESIGN

Women who were planning to undergo stress-incontinence surgery were invited to participate in the trial. Eligibility requirements included documented pure or predominant symptoms of stress incontinence for at least 3 months and a positive standardized urinary stress test.

Details of the study methods have been published previously.[15] All study procedures were approved by the institutional review board at each participating clinical center, and written consent was obtained from all women before enrollment. Randomization was performed in the operating room after anesthesia induction with the use of a permuted-block randomization schedule with stratification according to clinical site. The patients were aware of study-group assignments postoperatively. An independent data and safety monitoring board oversaw the progress, interim results, and safety of the study.

Formal interim time-to-event analyses of the primary outcome of overall success were planned for three time points, with the use of an O'Brien–Fleming stopping boundary, and were conducted when 19%, 44%, and 76% of failures had occurred. Although the test statistic at the third analysis crossed the stopping boundary in favor of the sling procedure, the protocol did not require stopping the trial when the boundary was crossed, and the data and safety monitoring board recommended that the study continue. No adjustment was made for these analyses.

Definitions of clinical terms, urodynamic nomenclature, and methods of evaluation of patients were uniform across all sites and in accordance with recommendations from the standardization committees of the International Continence Society.[5,16] Key elements of the two surgical procedures were standardized among all participating surgeons and included the use of preoperative antibiotics, skin-incision length, number and type of Burch sutures, fascial-sling length and width, and cystoscopic evaluation of the bladder. Because these procedures are frequently performed in conjunction with surgery for pelvic prolapse, abdominal and vaginal approaches for both pelvic prolapse repair and hysterectomy were permitted. However, surgeons were required to declare before randomization which concomitant procedures would be performed.

The two primary outcomes were composite measures of success in terms of overall urinary-incontinence measures and of stress-incontinence measures specifically. Overall treatment success was defined as no self-reported symptoms of urinary incontinence, an increase of less than 15 g in pad weight during a 24-hour pad test, no incontinence episodes recorded in a 3-day diary, a negative urinary stress test (no leakage noted on

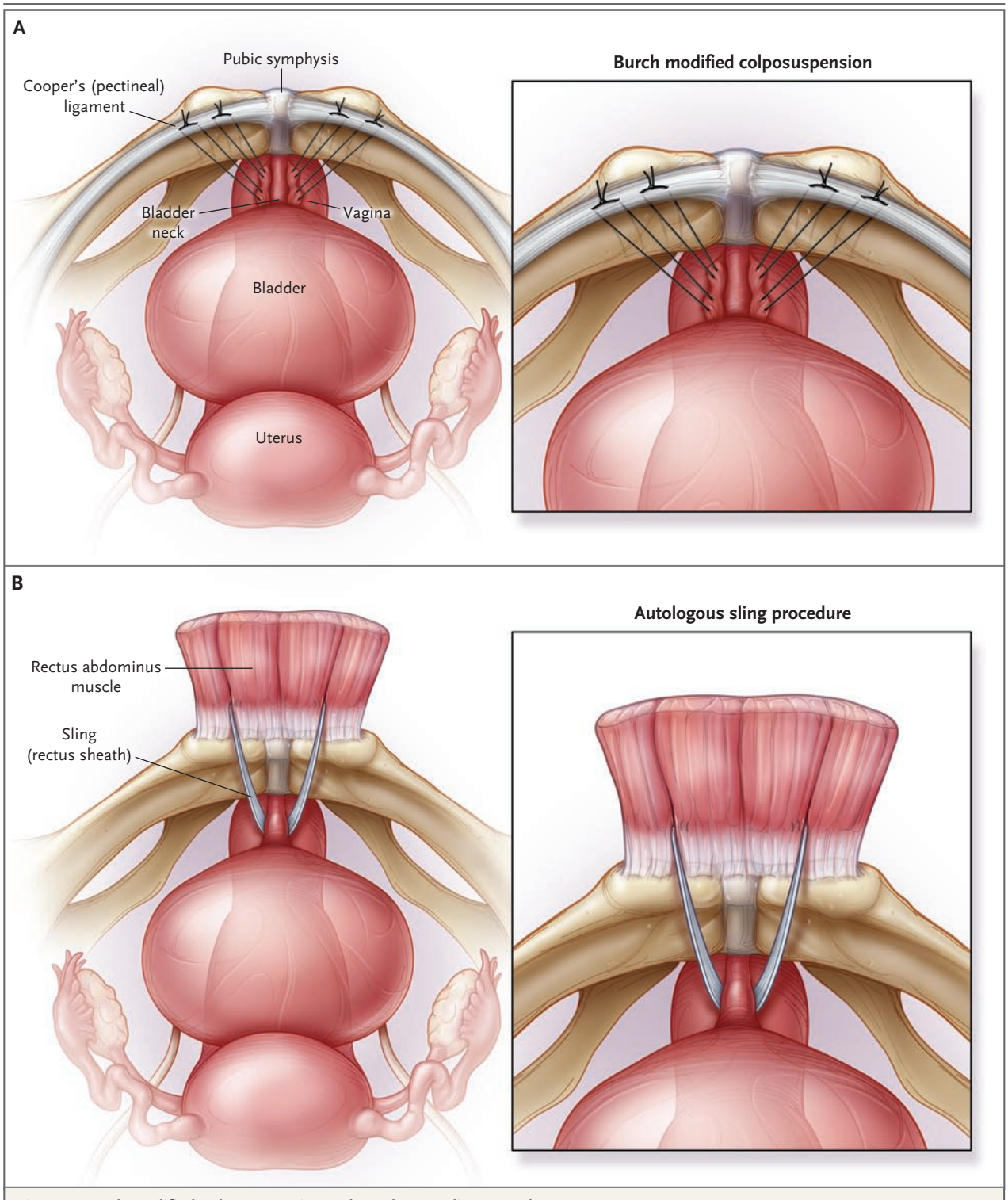

Figure 1. Burch Modified Colposuspension and Autologous Sling Procedure.

In the Burch procedure (Panel A), permanent sutures are placed in the anterior vaginal wall at the level of the bladder neck and proximal urethra and are then sutured to the iliopectineal ligament. In the autologous sling procedure (Panel B), a strip of rectus fascia is harvested, and permanent sutures are placed at its two ends. The sling is placed beneath the proximal urethra through a vaginal incision. The two ends of the sling are passed behind the pubic bone to the anterior abdominal wall, where they are secured, either to each other or to the rectus fascia.

examination during cough and Valsalva maneuvers at a standardized bladder volume of 300 ml), and no retreatment for urinary incontinence (including behavioral, pharmacologic, and surgical therapies). Since the study surgeries are intended to correct symptoms of stress incontinence without necessarily improving concomitant urge incontinence and the voiding diary and pad test do not differentiate between urge-incontinence and stress-incontinence events, the definition of success specific to stress incontinence was limited to no self-reported symptoms of stress incontinence, a negative stress test, and no retreatment for stress incontinence.

Data were collected preoperatively and postoperatively at 6 weeks and at 3, 6, 12, 18, and 24 months by means of interview and clinical examination. Baseline measures included sociodemographic characteristics; risk factors for urinary incontinence, including a high body-mass index, a history of vaginal childbirth, and previous surgery for urinary incontinence; quality of life specific to urinary incontinence[17]; clinical characteristics of urinary incontinence, including current behavioral or pharmacologic therapy, self-reported urinary-incontinence symptoms on a validated questionnaire distinguishing stress leakage from urge leakage,[18] quantity of urine leakage on a pad test,[19] and the number of incontinence episodes as recorded in a 3-day voiding diary[20]; findings on physical examination, including urethral hypermobility as measured by the Q-tip test[21] and pelvic-organ prolapse[22]; and urodynamic evaluation, including the presence of urodynamic stress incontinence and detrusor-overactivity incontinence.

The principal investigator at each site reported adverse events to the adverse-events committee, which comprised four investigators who were unaware of site-specific information. In certain cases, the descriptive details of the adverse event may have made it possible to discern the randomized surgical procedure. All adverse events were assigned a severity code according to a modified version of the classification system developed by Dindo and colleagues.[23] This system, which has been validated for use among surgical patients, classifies the severity of an event into one of four levels on the basis of the clinical measures taken to treat that event.

Postoperative urge incontinence was defined as treatment of clinically diagnosed new-onset or persistent urge incontinence after the 6-week follow-up visit. Adequacy of voiding was assessed and categorized dichotomously at hospital discharge and again 6 weeks after surgery. Voiding dysfunction was defined by the need for surgical revision to facilitate bladder emptying or the use of any type of catheter after the 6-week visit.

Patient satisfaction was assessed at 24 months with the question "How satisfied or dissatisfied are you with the result of bladder surgery related to urine leakage?" Patients rated their overall satisfaction, choosing one of five options that ranged from "completely satisfied" to "completely dissatisfied." Patients who answered that they were either "completely satisfied" or "mostly satisfied" were classified as being satisfied with the outcome.

STATISTICAL ANALYSIS

We calculated that 260 women per group would provide a power of 80% to detect a 12% difference between study groups (60% vs. 72%) with the use of a two-sided alternative hypothesis at a significance level of 5%. To allow for attrition and missed visits, we recruited a total of 655 women. Treatment success was assessed at follow-up visits every 6 months. If a treatment failed between scheduled visits, it was considered to have failed at the next visit. Data for women whose treatment was not known to have failed but who had not completed all assessments at the 24-month visit were censored at the last visit on which all failure assessments were complete.

For both outcome measures, we compared the success rates in the two groups at 24 months with the use of time-to-event methods for interval censored data.[24] We used Kaplan–Meier product-limit analysis to estimate the success rates at 24 months in the two groups and compared the treatment-failure distributions in the two groups, controlling for stratification by clinical site, with the use of the log-rank test. To determine whether concomitant surgery might have had an effect on the results, we tested the interaction between treatment group and concomitant surgery with the use of the Weibull accelerated failure-time model. All analyses were carried out with SAS statistical software, version 9.2 (SAS Institute).

RESULTS

PATIENTS

From February 2002 to June 2004, we screened 2405 women for trial eligibility (Fig. 2). Of these women, 556 were ineligible, 1193 declined to

participate or withdrew consent, and 1 died before randomization. A total of 655 women were randomly assigned to a study procedure: 326 to undergo the sling procedure and 329 to undergo the Burch procedure. One woman did not undergo the assigned treatment (Burch procedure), and four women were found to be ineligible after randomization (one assigned to the sling procedure and three assigned to the Burch procedure). A total of 520 women (79%) — 265 in the sling group (81%) and 255 in the Burch group (78%) — either were assessed for treatment success at the 24-month visit or were deemed to have had a treatment failure before that visit.

Women in the two surgical groups were similar in demographic, anthropometric, clinical, and urodynamic-study characteristics (Table 1). The frequency of previous surgery for urinary incontinence was similar in the two groups (13% in the sling group and 15% in the Burch group). The rates of concomitant surgery for pelvic prolapse (including anterior and posterior vaginal repairs, apical suspension procedures, and hysterectomy) were also similar in the two groups (55% in the sling group and 48% in the Burch group). The sling and Burch groups had similar estimated blood loss during the procedure (229 ml and 238 ml, respectively) and similar operative times (136 minutes and 138 minutes, respectively).

Women in the sling group had 24-month cumulative rates of success that were significantly higher than those in the Burch group, with overall success rates of 47% versus 38% ($P=0.01$), and rates of success specific to stress incontinence of 66% versus 49% ($P<0.001$) by the log-rank test of equality of distributions with adjustment for site (Fig. 3). There was no clinically or statistically significant interaction effect of concomitant surgery and treatment group on either outcome ($P=0.74$ for overall success, and $P=0.84$ for success specific to stress incontinence).

The rate of occurrence of each component of the composite measure of success, as a percentage of patients with complete follow-up assessments, differed according to the treatment group (Fig. 4). These differences reflected the fact that the sling group had lower rates of reported symptoms related to stress incontinence, positive stress tests, and retreatment of stress incontinence than did the Burch group.

There was no significant difference between the sling and Burch groups in the percentage of patients who had serious adverse events (13% and 10%, respectively; $P=0.20$) (Table 2). However, surgical procedures to reduce voiding symptoms or improve urinary retention were performed exclusively in the sling group, in which 19 patients underwent 20 such procedures. Adverse events were more common in the sling group than in the Burch group (63% vs. 47%, $P<0.001$), with 415 events among 206 women in the sling group, as compared with 305 events among 156 women in the Burch group. This difference was due primarily to urinary tract infections; 157 women in the sling group (48%) had 305 events and 105 women in the Burch group (32%) had 203 events. When urinary tract infections were excluded, the rates of adverse events were similar in the two groups.

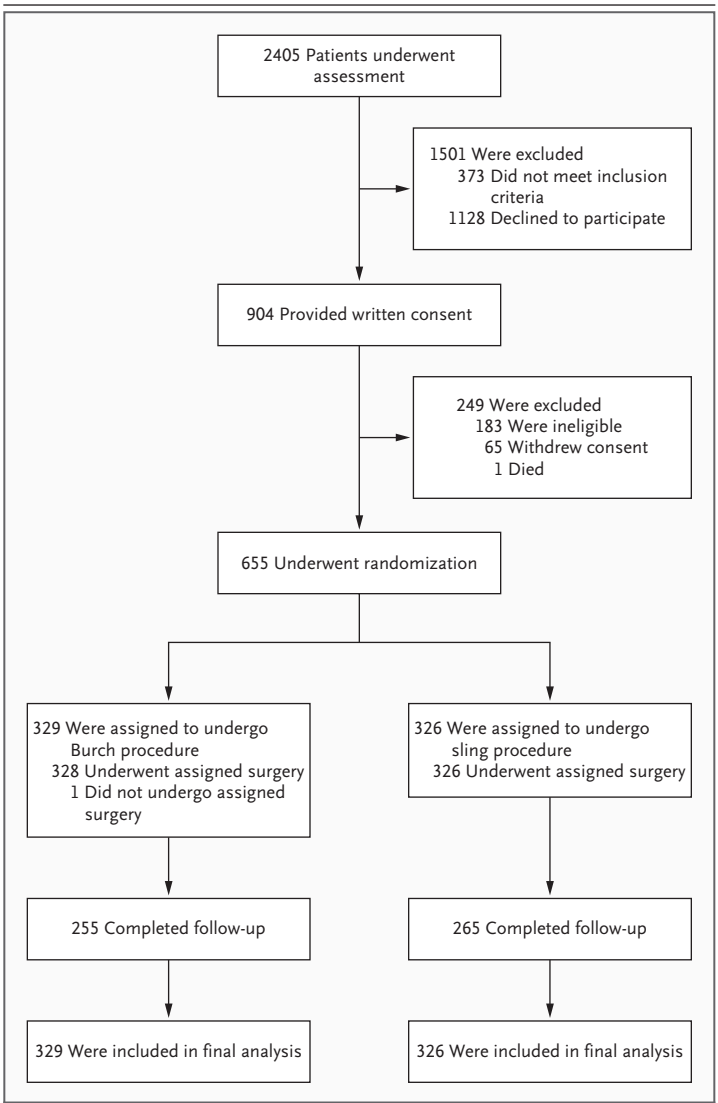

Figure 2. Enrollment and Outcomes.

Table 1. Selected Characteristics of the Patients.*

Variable	Burch Procedure (N=329)	Sling Procedure (N=326)	P Value
Demographic characteristics			
Age (yr)	52.2±10.5	51.6±10.1	0.47
Racial or ethnic group (%)†			0.04
Hispanic	9	13	
Non-Hispanic white	75	71	
Non-Hispanic black	5	9	
Non-Hispanic other	11	7	
Marital status (%)			0.56
Married or living with partner	69	67	
Not married	31	33	
Education (%)			0.79
High school or less	33	36	
Some training after high school	40	39	
College degree or more	27	25	
Household income (%)			0.65
<$20,000	21	17	
$20,000–49,999	29	31	
$50,000–79,999	21	21	
≥$80,000	29	31	
Risk factors			
Body-mass index	29.7±6.1	30.3±6.1	0.26
No. of vaginal deliveries (%)			0.14
0	8	10	
1–2	46	39	
≥3	46	51	
Previous incontinence surgery (%)	15	13	0.46
Smoking status (%)			0.04
Never smoked	59	49	
Former smoker	29	34	
Current smoker	12	17	
Hormone-replacement therapy (%)			0.66
Yes	35	32	
No	36	36	
No, premenopausal	29	32	

The distribution of time to return to normal voiding differed significantly between the two groups (P<0.001). At the time of hospital discharge, fewer patients in the sling group than in the Burch group had voiding with a residual volume of less than 100 ml (44% vs. 58%), and the difference persisted at 6 weeks (86% vs. 97%). Voiding dysfunction was more common in the sling group than in the Burch group (14% vs. 2%, P<0.001). More patients were treated for postoperative urge incontinence in the sling group than in the Burch group (87 patients [27%] vs. 65 patients [20%], P=0.04). The difference in urge incontinence was due to differences in the proportion of patients treated for persistent urge incontinence (79 patients in the sling group [24%] vs. 59 patients in the Burch group [18%]) rather than to differences in the proportion with new-onset urge incontinence (11 patients [3%] in both groups).

Treatment-satisfaction rates for the 480 subjects who answered the satisfaction question at 24 months were significantly higher in the sling

Table 1. (Continued.)

Variable	Burch Procedure (N=329)	Sling Procedure (N=326)	P Value
Clinical characteristics			
Quality of life‡			
Total score on Urogenital Distress Inventory	150.3±49.9	151.6±47.4	0.73
Total score on Incontinence Impact Questionnaire	173.2±99.2	169.7±103.4	0.66
Pad test weight (g)	42.4±61.2	44.7±94.3	0.71
Incontinence episodes per day (no.)	3.3±3.1	3.1±2.9	0.52
Urinary-incontinence symptom score§			
Stress score	19.5±4.5	19.2±4.7	0.37
Urge score	6.6±3.9	6.3±3.9	0.44
Prolapse stage (%)¶			
0 or 1	26	24	0.60
2	59	59	
3 or 4	15	17	
Q-tip test (degree)			
Resting angle	15.6±17.1	15.2±18.3	0.77
Straining angle	61.1±19.3	59.3±17.3	0.23
Difference between straining angle and resting angle	45.5±19.1	44.1±17.3	0.35
Urodynamic studies (%)			
Stress incontinence			0.64
Yes	89	89	
No	9	10	
Invalid study	2	1	
Valsalva leak point pressure‖			
≤60 cm of H_2O	4	3	0.46
Change of ≤60 cm of H_2O	22	20	0.54
Detrusor overactivity	11	7	0.10
Surgical characteristics			
Concomitant surgery (%)**			0.19
None	44	40	
Prolapse surgery with repair of anterior vaginal wall (with or without other repair)	17	23	
Prolapse surgery without repair of anterior vaginal wall (including posterior wall and apex)	31	32	
Other nonprolapse surgery††	8	6	

* Plus–minus values are means ±SD. Body-mass index is the weight in kilograms divided by the square of the height in meters. Percentages may not total 100 because of rounding.
† Racial or ethnic group was reported by the patients.
‡ Scores on the Urogenital Distress Inventory range from 0 to 300, with higher scores indicating greater distress. Scores on the Incontinence Impact Questionnaire range from 0 to 400, with higher scores indicating greater impact.[17]
§ Symptom scores are the sum of responses to nine questions regarding stress symptoms (with scores ranging from 0 to 27 and higher scores indicating greater severity) and six questions regarding urge symptoms (with scores ranging from 0 to 18 and higher scores indicating greater severity) adapted from the Medical, Epidemiological, and Social Aspects of Aging questionnaire.[18]
¶ Prolapse staging is based on the methods of the Pelvic Organ Prolapse Quantification system.[22]
‖ Valsalva leak point pressure refers to the vesical pressure at the time of leakage. The change in the Valsalva leak point pressure is the vesical pressure at the time of leakage minus the baseline vesical pressure.
** Concomitant prolapse repairs included repair of the anterior vaginal wall (anterior colporrhaphy and paravaginal repair), posterior colporrhaphy, apical suspension procedures (sacrospinous ligament suspension, uterosacral ligament suspension, and sacrocolpopexy), enterocele repair, and hysterectomy.
†† Other concomitant surgeries included anal-sphincter repair, tubal ligation, and abdominoplasty.

group than in the Burch group (86% vs. 78%, P=0.02).

DISCUSSION

At 24 months, the pubovaginal fascial sling had significantly higher rates of success — both overall and specific to stress incontinence — than did the Burch colposuspension in women with predominant stress incontinence. These findings were not modified by performance of concomitant surgery for pelvic-organ prolapse. In addition, the frequency of surgical retreatment for stress incontinence was greater in the Burch group than in the sling group. Success rates declined steadily over the 2-year follow-up period, which confirmed previous observations[25,26] and underscored the need for long-term follow-up in these patients.

However, the higher success rates in the sling group were offset by higher rates of urinary tract infection, urge incontinence, voiding dysfunction, and the need for surgical revision to improve voiding. The increased efficacy and greater morbidity of the sling procedure confirm and quantify the results of previous systematic reviews[27-29] and may explain some of the reluctance in the past to use this procedure as a primary surgical treatment for stress incontinence.[14]

Our large, randomized surgical trial comparing the fascial-sling procedure with the Burch procedure had a robust 24-month follow-up with the use of standardized definitions, procedures, and methods of evaluation to assess a variety of outcome measures and comprehensive postoperative morbidity. The absence of such information to date has precluded rigorous assessment of surgical outcomes for this condition.[30,31] Reported success rates of surgery have varied widely.[27,28] Factors contributing to this variation have included the lack of standardized outcome measures, differences in the baseline characteristics of the study populations, and the length of follow-up.[32,33]

Success rates that are based on reporting by patients are consistently lower than those based on physician-reported measures.[34,35] Current research guidelines emphasize the importance of evaluating treatment efficacy with composite out-

Table 2. Adverse Events.*

Event	Burch Procedure (N=329)	Sling Procedure (N=326)	P Value†
	no. (%)		
Serious adverse events‡			
Patients with event	32 (10)	42 (13)	0.20
Total events	39	47	
Genitourinary	22	30	0.12
Ureteral injury	2	0	
Ureterovaginal fistula	1	0	
Incidental vaginotomy	1	0	
Incidental cystotomy	10	2	
Erosion of suture into bladder	1	0	
Recurrent cystitis, leading to diagnostic cystoscopy	5	6	
Pyelonephritis	1	1	
Catheter complication	1	1	
Voiding dysfunction leading to surgical revision	0	20	
Pelvic pain	0	2	0.25
Bleeding	3	1	0.62
Wound complication requiring surgical intervention	13	11	0.83
Gastrointestinal	1	1	1.00
Respiratory distress requiring intubation	0	1	0.50
Laryngospasm requiring reintubation	0	1	0.50

Table 2. (Continued.)

Event	Burch Procedure (N=329)	Sling Procedure (N=326)	P Value†
	no. (%)		
Adverse events§			
Patients with event	156 (47)	206 (63)	<0.001
Total events	305	415	
Genitourinary	203	305	<0.001
Cystitis	202	299	
Pyelonephritis	1	6	
Vascular or hematologic	5	9	0.29
Deep-vein thrombosis	0	1	
Bleeding	5	8	
Wound complication not requiring surgical intervention	69	71	0.69
Gastrointestinal	7	8	0.80
Pulmonary	10	9	1.00
Neurologic	6	5	1.00
Cardiovascular	0	2	0.25
Allergic (hives, itching)	0	2	0.25
Constitutional	3	0	0.25
Dermatologic (rash, erythema)	2	4	0.45

* The severity grade was determined by using a slightly modified version of the Dindo classification system,[23] which is based on the level of therapy required to treat an event: grade I, no pharmacologic, surgical, or radiologic intervention (allowed therapeutic regimens include antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy); grade II, pharmacologic treatment with drugs other than those allowed for grade I complications (including antibiotics, blood transfusions, and total parenteral nutrition); grade III, surgical, endoscopic, or radiologic intervention; grade IV, life-threatening complication requiring intensive care management; and grade V, death. Serious adverse events were defined as a severity of grade III, grade IV, or grade V; no grade V events occurred in either group.

† P values were calculated with the use of Fisher's exact test.

‡ Catheter complications included clot retention requiring cystoscopy (sling group, 1 patient) or a suprapubic tube stitched in place (Burch group, 1 patient). Wound complications requiring surgical intervention included incisional hernia (Burch, 5 patients; sling, 3), seroma or hematoma (Burch, 2; sling, 3), infection (Burch, 2; sling, 2), abscess (Burch, 1; sling, 1), and vaginal wound revision (Burch, 3; sling, 2). Gastrointestinal complications included 1 rectal injury (in the sling group) and 1 episode of constipation requiring surgical disimpaction (in the Burch group).

§ Cystitis was defined as culture-proven bladder infection or, in the absence of a culture, clinical suspicion of a bladder infection that resulted in treatment. Wound complications not requiring surgical intervention included 2 sling exposures (visualization of the sling material in the vagina), incisional hernia (Burch group, 2; sling group, 1), superficial wound-edge separation (Burch, 10; sling, 5), seroma or hematoma (Burch, 13; sling, 11), infection (Burch, 31; sling, 21), and granulation tissue or stitch granulomas (Burch, 13; sling, 31). Gastrointestinal events included ileus (Burch, 5; sling, 2) and other complications (anal fissure, constipation, prolapsed hemorrhoids, nausea and vomiting, abdominal pain, rectal bleeding, and pseudomembranous colitis) (Burch, 2; sling, 6). Pulmonary events included atelectasis (Burch, 4; sling, 6), pneumonia (Burch, 2; sling, 1), pulmonary edema (Burch, 1; sling, 1), and other complications (anesthesia airway difficulty resulting in rescheduling of surgery, oversedation, upper respiratory infection) (Burch, 3; sling, 1). Neurologic complications included sciatica (Burch, 1; sling, 1), numbness or weakness or pain temporally related to surgery (Burch, 4; sling, 3), and vertigo or vestibular neuritis (Burch, 1; sling, 1). In the sling group, cardiovascular events included bradycardia treated in the recovery room (1) and junctional rhythm ruled out for myocardial infarction (1). In the Burch group, constitutional events included fever of unknown origin (2) and hypokalemia (1).

come measures that include both subjective and objective efficacy measures as well as an assessment of morbidity.[36-38] Success rates in our trial were low, as compared with those in previous studies.[9,10] This finding may be related to our use of composite outcome measures, resulting in a stricter definition of success. The substantial variation in failure rates among studies using single-component measures supports the use of composite outcome measures[32] and highlights the lack of concordance among several traditional measures.

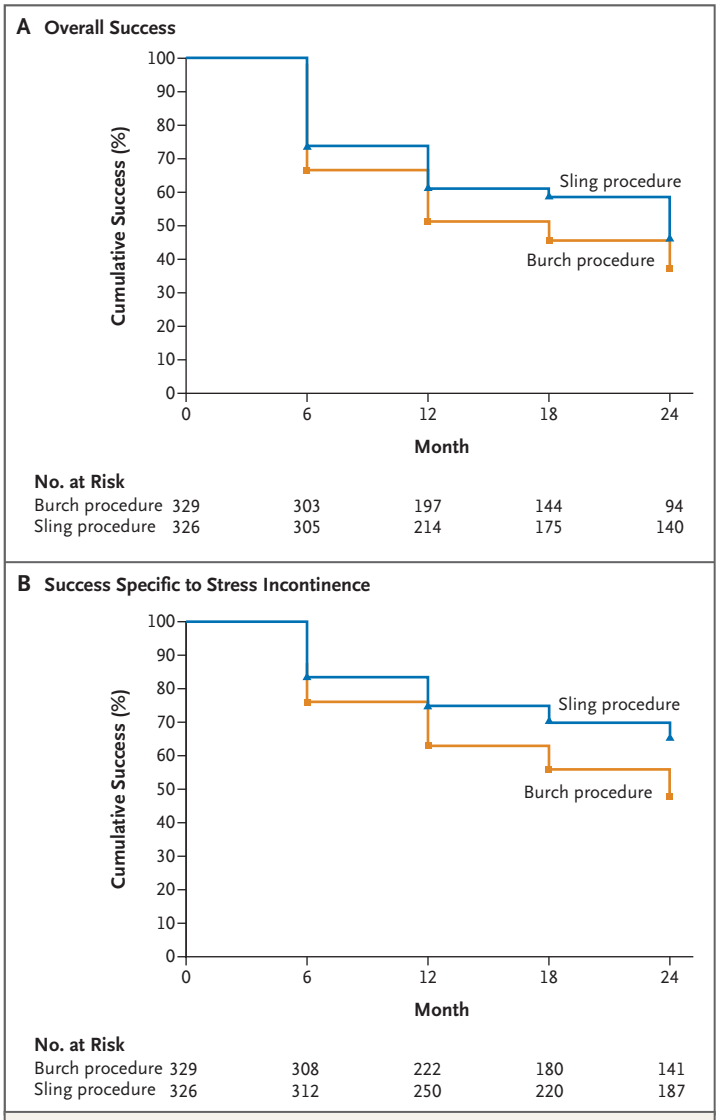

Figure 3. Kaplan–Meier Curves for Success of Surgical Treatment for Urinary Incontinence at 24 Months among All Patients.

Panel A shows the overall treatment success for urinary-incontinence measures (P=0.01), and Panel B shows success in terms of measures of stress incontinence specifically (P<0.001), with both comparisons based on the log-rank test of equality of distributions, with adjustment for site.

Our finding that the two procedures had similar success rates as measured by pad tests and voiding diaries may reflect the higher number of patients with symptoms of urge incontinence in the sling group, since these two measures cannot differentiate stress incontinence from urge incontinence. It is likely that we underestimated the rate of postoperative urge incontinence, since our definition was restricted to patients who received treatment for this condition. This factor may explain in part why only 3% of the patients in our trial had new-onset urge incontinence, a rate that is at the low end of the range reported by others.[29,39]

The higher rate of urinary tract infections reported in the sling group, as compared with the Burch group, may be related to a delayed return to adequate voiding and a prolonged need for catheterization in the sling group. Our definition of urinary tract infection did not require a positive urine culture, and it is possible that some patients received empirical antibiotic therapy for symptoms alone, leading us to overestimate the true incidence of postoperative urinary tract infection in either or both groups. For instance, the higher rate of urge incontinence identified in the sling group may have led to more false diagnoses of urinary tract infection in that group.

All the patients in our study received care in tertiary care centers, and the study population included only women with urethral hypermobility and pure or stress-predominant incontinence. Whether the results can be generalized to other groups of women is uncertain. Both the patients and the health care providers were aware of study-group assignments, and it is possible that bias affected the measurement of some outcomes.

Just over half the women underwent concomitant surgery for pelvic-organ prolapse, a proportion consistent with that in other studies.[8] Although we did not find any material differences in success rates on the basis of concomitant surgery, such procedures could potentially influence the number of adverse events identified in both groups.

The sling group also had higher satisfaction rates than did the Burch group, a difference that was consistent with the success rates. However, satisfaction rates were higher in both groups than were success rates, indicating that satisfaction was influenced by factors beyond the resolution of incontinence symptoms. Further analyses are needed to assess the relationships among the satisfaction reported by patients, improvement in the quality of life, and outcome measures described here.

New surgical procedures for stress incontinence continue to be introduced into clinical practice without evaluation of their efficacy and safety in well-designed, randomized clinical trials.[27,28] There has been a recent transition from

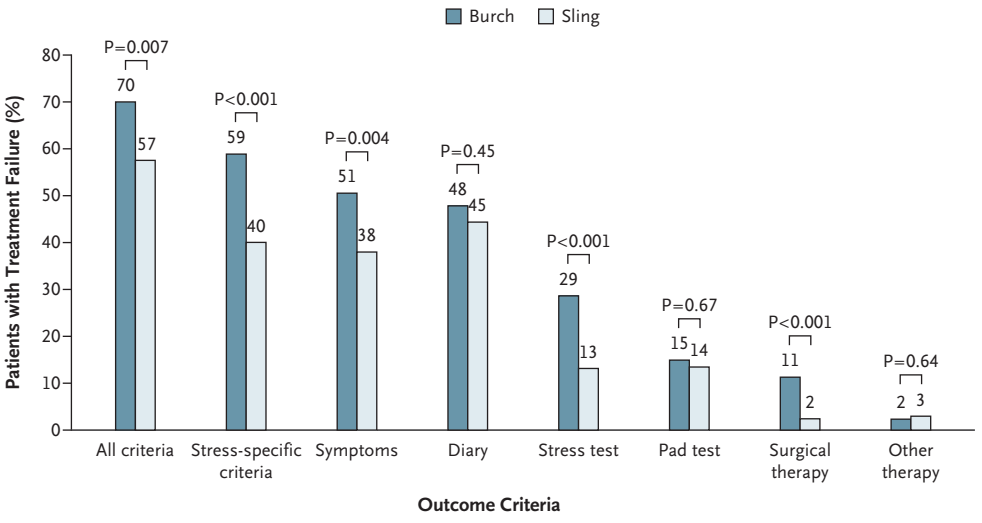

Figure 4. Proportion of Patients with Treatment Failure at 2 Years, According to Overall Composite Criteria, Composite Criteria Specific to Stress Incontinence, and Other Criteria.

Results are given for 520 patients — 255 who underwent the Burch procedure and 265 who underwent the sling procedure — for whom complete data were available at 24 months. P values are crude unadjusted comparisons of percentages.

the fascial sling and Burch procedure to the newer midurethral synthetic sling. A previous randomized surgical trial comparing the midurethral sling with the Burch procedure showed similar efficacy of the two procedures,[32,40] although that study has been criticized for being underpowered. No randomized trials have compared the midurethral sling with the autologous fascial sling. The relative frequency with which these procedures are performed in the United States is difficult to assess because they have identical procedural codes. Rigorous comparative trials are needed to assess the efficacy and safety of these novel surgical techniques as compared with the efficacy and safety of the procedures studied in our trial.

The number of women undergoing surgical therapy for stress incontinence is increasing, and this trend is likely to continue as the population ages. Our data show that the pubovaginal fascial sling has significantly higher efficacy than the Burch abdominal colposuspension at 24 months in women with predominant stress incontinence, but such success comes at the cost of more complications. Clinicians should discuss such trade-offs when making recommendations to patients regarding the optimal procedure and should emphasize that complete resolution of incontinence symptoms after surgery is unlikely.

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APPENDIX

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EXHIBIT EE

UROGYNECOLOGY

One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse

Andrew I. Sokol, MD; Cheryl B. Iglesia, MD; Bela I. Kudish, MD; Robert E. Gutman, MD; David Shveiky, MD; Richard Bercik, MD; Eric R. Sokol, MD

OBJECTIVE: The purpose of this study was to show 12-month outcomes of a randomized trial that compared vaginal prolapse repair with and without mesh.

STUDY DESIGN: Women with stage ≥2 prolapse were assigned randomly to vaginal repair with or without mesh. The primary outcome was prolapse stage ≤1 at 12 months. Secondary outcomes included quality of life and complications.

RESULTS: All 65 evaluable participants were followed for 12 months after trial stoppage for mesh exposures. Thirty-two women had mesh repair; 33 women had traditional repair. At 12 months, both groups had improvement of pelvic organ prolapse-quantification test points to similar recurrence rates. The quality of life improved and did not differ between groups: 96.2% mesh vs 90.9% no-mesh subjects reported a cure of bulge symptoms; 15.6% had mesh exposures, and reoperation rates were higher with mesh.

CONCLUSION: Objective and subjective improvement is seen after vaginal prolapse repair with or without mesh. However, mesh resulted in a higher reoperation rate and did not improve 1-year cure.

Key words: exposure, prolapse repair, randomized trial, vaginal mesh

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The use of mesh to augment vaginal prolapse repairs has become a topic of considerable debate over the past few years. Proponents of mesh use point to the up to 30% reoperation rate quoted in some studies for traditional vaginal prolapse repair surgeries.[1] Initial retrospective and prospective cohort studies showed high success rates with few complications.[2-7] A few published studies have shown some benefit of synthetic mesh-augmented procedures over traditional repairs for the anterior compartment.[8,9] However, the rise in mesh augmentation led to increased reports of mesh-related complications, which prompted a Food and Drug Administration advisory about the use of mesh in pelvic surgery.[10] Given the rise in litigation surrounding mesh repairs, particularly after the Food and Drug Administration advisory, some investigators recently have suggested that separate consent forms be used for prolapse repair that involves mesh.[11] This makes the analysis of the potential risks and benefits of mesh for vaginal prolapse repair more important than ever.

Currently, no double-blind randomized controlled trials (RCTs) have evaluated the long-term effectiveness of these procedures for multicompartment prolapse. The primary objective of this double-blind, multicenter RCT was to test the hypothesis that the addition interpositional polypropylene mesh improves the 1-year objective treatment success (pelvic organ prolapse–quantification [POP-Q] stage ≤1) of vaginal reconstructive surgery for pelvic organ prolapse compared with traditional vaginal reconstructive surgery without mesh. Secondary objectives were to compare patient satisfaction, quality-of-life (QOL) variables, short-term and long-term complications, vaginal caliber and morbidity that were related to mesh use between the 2 arms of the trial.

Materials and Methods

This multicenter, double-blind RCT was conducted by 6 fellowship-trained pelvic reconstructive surgeons at Washington Hospital Center, Stanford University and Yale University. Institutional review board approval was obtained at each site, and all

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R.B. has received payment from Gynecare for lectures, consulting, and proctoring surgical cases within the last 3 years. The other authors report no conflict of interest. Prolift mesh kits for this study were donated by Ethicon Women's Health and Urology, Somerville, NJ.

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women provided written informed consent to participate. A detailed description of the study methods and trial design has been published previously.[12] Briefly, women with POP-Q prolapse stages 2-4 were assigned randomly to traditional vaginal prolapse repair without mesh (primarily combined anterior/posterior colporrhaphy and uterosacral ligament suspension) or vaginal colpopexy with mesh (Prolift; Ethicon Women's Health and Urology, Somerville, NJ). Random assignment occurred with computer-generated random numbers that were stratified for presence or absence of a uterus. Opaque sealed envelopes were opened in the operating room after the patient received anesthesia. The research study nurse coordinator at each site, other research staff, and the patient were masked to the treatment assignment. The primary outcome measure was objective treatment success (POP-Q stage ≤1) at 12 months. Secondary outcome measures included QOL variables, lower urinary tract function, vaginal caliber, and complication rates. Stopping criteria were set with the use of a .001 level of significance and a >15% observed mesh exposure rate, >1% mesh infection rate, >1% fistula formation, and >5% rate of de novo dyspareunia.

Surgery

The surgical techniques in both the mesh and no-mesh groups have been described previously.[12] The techniques for the procedures were standardized for uniformity and included choice of sutures for uterosacral ligament suspension or sacrospinous fixation (combination delayed absorbable polydioxanone sutures [Ethicon, Somerville, NJ]) and permanent polytetrafluoroethylene sutures (Gore-tex; W.L. Gore & Associates, Flagstaff, AZ) and a choice of vaginal mesh kit (Prolift). Apical suspension with uterosacral ligament suspension or sacrospinous suspension (no-mesh arm) vs total vaginal mesh (total Prolift) or modification (anterior Prolift with the insertion of the posterior arms through the sacrospinous ligament; mesh arm) was performed if the cuff or posterior fornix was <3 cm proximal to hymeneal remnant (point C and D ≥ –3) or if the surgeon believed there to be the need for additional apical support. The uterosacral ligament suspension was conducted as described by Shull et al[13]; the Prolift procedures were performed in accordance with product recommendations. To maintain patient masking, steristrips were placed on the vulva after the surgery (to mimic dressings placed after Prolift), regardless of treatment assignment.

All surgeons were fellowship trained and had performed >30 vaginal colpopexy procedures with uterosacral and sacrospinous ligaments and a minimum of 10 Prolift procedures before patients were enrolled in the trial.

Outcome measures

The primary outcome measure for objective treatment success was overall POP-Q stage ≤1 (descent at >1 cm proximal to the hymen) at 1 year. The need for additional surgical treatment or pessary placement for recurrent prolapse at any time after the initial procedure also constituted treatment failure. These definitions conform to the recommendations from the National Institutes of Health Terminology Workshop for Researchers in Female Pelvic Floor Disorders.[14]

The secondary outcome measures for objective treatment success consisted of anterior, apical, and posterior prolapse stage ≤1 (Ba, Bp, and C >1 cm proximal to the hymen) at 1 year. POP-Q measurements were obtained at 3 and 12 months and yearly thereafter by blinded examiners who had been trained in the performance of POP-Q. For the secondary outcomes, each compartment was analyzed separately for cure. Socioeconomic characteristics, risk factors, and preoperative prolapse severity were investigated as possible factors that could influence the outcome in each arm. Impact on QOL was assessed with validated questionnaires. Preoperative QOL questionnaires were completed at enrollment, at 3 and 12 months, and yearly thereafter. A research nurse coordinator updated contact information, medical history, and adverse events during a 6-month postoperative telephone interview. The following validated QOL tools were used: the SF-12[15] with both Physical Component Summary and Mental Component Summary, the short forms of Pelvic Floor Distress Inventory that included subscales of Pelvic Organ Prolapse Distress Inventory, the Colorectal Anal Distress Inventory, the Urogenital Distress Inventory, the Pelvic Floor Impact Questionnaire with the corresponding Colorectal Anal Impact Questionnaire, the Pelvic Organ Prolapse Impact Questionnaire and the Urinary Impact Questionnaire,[16] the Prolapse and Incontinence Sexual Questionnaire,[17] the Patient Global Impression of Improvement,[18] and the Patient Global Impression of Severity.[18]

Perioperative measures of morbidity that included operative time, estimated blood loss, and intra- and postoperative complications were recorded at the completion of surgery, at hospital discharge, and at the 6-week postoperative visit. Complications were categorized with a modification of the Dindo Classification.[19]

Women who completed at least approximately 1 year of follow-up evaluation were compared with respect to changes in vaginal caliber that was measured by a ring pessary (diameter in centimeters) at baseline, at 3 and 12 months, and yearly thereafter; to vaginal volume (formula: volume of a cylinder πr^2total vaginal length; cubed centimeters), and POP-Q measurements. One-year Prolapse and Incontinence Sexual Questionnaire-12 scores and dyspareunia for sexually active women were compared with baseline.

Statistical methods

Methods of data analysis and sample size calculation have been described previously.[12] SPSS software for Windows (version 16; SPSS Inc, Chicago, IL) was used for data management and statistical analysis. A .05 significance level was used for all statistical tests. No 1-sided tests were done. For vaginal caliber and sexual function, Mann-Whitney, χ^2, Fisher's exact, and Spearman correlation tests were used for statistical analysis. Survival analysis methods were used to analyze times to recurrence, because these variables had censored data. The log-rank test and Cox proportional hazards regression were used to compare independent groups with respect to recurrence and exposure. Means are presented as mean ± standard deviation or mean (range). Me-

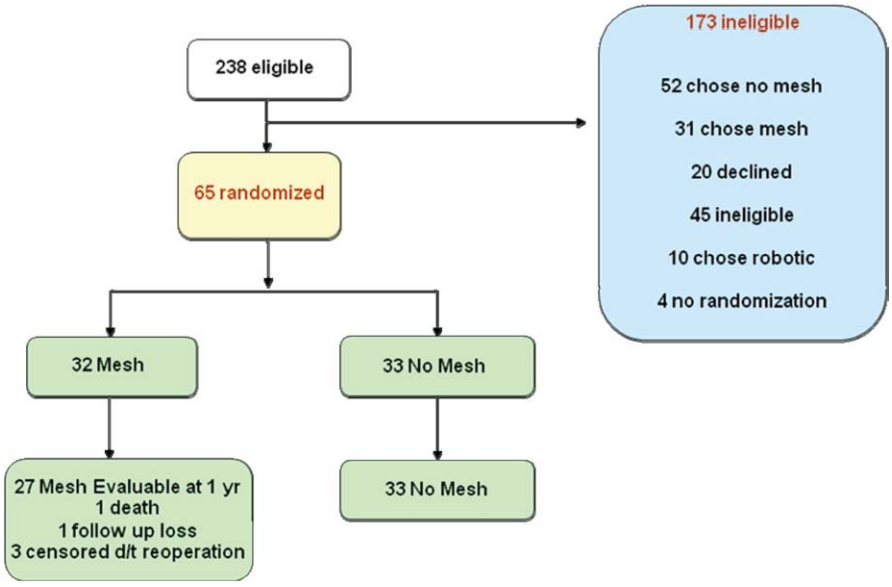
dians are presented as median (range). Data that were obtained after repeat surgery for prolapse recurrence were not included in the analyses, which was done to eliminate the chance that data would be skewed toward improved outcomes after repeat surgery.

RESULTS

Recruitment began on January 3, 2007, and continued until August 1, 2009, at which time the study was halted because of predetermined criteria for vaginal mesh exposure at a mean follow-up time of 7.2 months (range, 2.1–14.7 months). Recruited patients were then observed until all evaluable participants (60/65; 92.3%) reached ≥12 months of follow up (mean, 14.7 months) with a POP-Q evaluation. Enrollment and disposition of the trial are summarized in the Figure. The conditions of 5 patients in the mesh arm were not evaluable at 12 months and were thus censored from the analysis: 1 patient died of a myocardial infarction after 3.7 months; 1 patient did not return for follow-up evaluation after 7.2 months, and 3 patients needed additional prolapse surgery at <12 months of follow up (4.6, 9.8, and 10.2 months). All patients in the no-mesh arm were evaluated at 12 months. Thirty-two subjects (49.2%) had mesh surgery; 14 of these subjects (44%) had undergone hysterectomy earlier. Thirty-three subjects (50.8%) had no-mesh surgery; 12 of these subjects (36%) had undergone hysterectomy earlier. Baseline characteristics did not differ significantly between these 2 groups (Table 1). With the exception of posterior repair that was performed more commonly in the no-mesh group (56% vs 82%; $P = .026$), similar procedures were performed concomitantly in each group.[12] Operative times were similar between the mesh (3.0 ± 0.8 hours) and no-mesh groups (3.1 ± 1.0 hours; $P = .53$). Estimated blood loss was also similar (mesh group, 124.5 ± 79.7 mL vs no-mesh group, 154.5 ± 107.1 mL; $P = .29$).

There was a statistically significant difference between the mesh and no-mesh groups with respect to months of follow up: the mesh group had a mean time of 13.2 ± 4.7 months and a median time of 12.2 months (range, 3.7–26.7 months); the no-mesh group had a mean time of 16.2 ± 5.4 months and a median time of 13.1 months (range, 11.6–27.7 months; $P = .037$). There were no statistically significant differences between the mesh and no-mesh groups with respect to the preoperative overall POP-Q stage or the preoperative POP-Q stage by points Ba, Bp, or C (Mann-Whitney test, $P = .31$ to .63). At approximately 12 months after the procedure, both groups had statistically significant improvements of POP-Q points C, Ba, and Bp ($P < .001$; $P = .002$).

FIGURE
The passage of participants through the randomized trial



d/t, due to.

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Objective recurrence

No statistically significant differences in overall recurrence (postoperative overall POP-Q stage ≥2; $P = .45$) or in recurrence by compartment were found between the mesh and no-mesh groups (Table 2). A total of 43 subjects (66.2%) had an objective recurrence of stage ≥2 prolapse in 20 of the mesh subjects (62.5%) compared with 23 of the no-mesh subjects (69.7%). Of the 43 recurrences, 33 recurrences (76.7%) were at or proximal to the hymeneal remnant: 15 of the mesh group (75.0%) vs 18 of the no-mesh group (78.3%; $P > .99$). Ten of the 43 recurrences (23.3%) were distal to the hymeneal remnant. Most recurrences involved the anterior compartment (15 mesh and 19 no-mesh subjects).

No statistically significant differences were found between the mesh and no-mesh groups with respect to anterior wall recurrence (postoperative POP-Q stage ≥2 at point Ba; $P = .30$) or posterior wall recurrence (postoperative POP-Q stage ≥2 at point Bp; $P = .66$). Fifteen of the mesh subjects (46.9%) vs 20 of the no-mesh subjects (60.6%) had an anterior wall recurrence ($P = .40$), and 7 subjects (21.9%) vs 6 subjects (18.2%) had a posterior wall recurrence ($P = .61$), respectively. Three months after the operation, the point Ba measurement was significantly better for the mesh group, even though overall anterior POP-Q stage recurrence was not significantly different.[11] At 12 months, however, the difference in point Ba was no longer statistically significant ($P = .077$). Only 1 subject had an apical recurrence (postoperative POP-Q point C at stage ≥2). This patient had a redundant 14-cm vagina, and the surgeon made the clinical decision to trim the excess epithelium and muscularis. Because of the

TABLE 1
Baseline characteristics of study participants

Characteristic	Group Mesh	No mesh	*P* value
Age, y[a]	64.4 ± 10.8	63.5 ± 8.9	.61
Race, n (%)			.70[b]
White	20 (62.5)	22 (66.7)	
African American	8 (25.0)	7 (21.2)	
Hispanic	3 (9.4)	3 (9.1)	
Asian	1 (3.1)	0	
Other	0	1 (3.0)	0
Postmenopausal, n (%)	30 (93.8)	31 (93.9)	1
Married, n (%)	20 (62.5)	21 (63.6)	.92
Educational level, n (%)			.40
<High school	0	2 (6.1)	
Completed high school	10 (31.3)	11 (33.3)	
College or graduate	22 (68.8)	20 (60.6)	0
Health insurance, n (%)			.54
Private	15 (46.9)	18 (54.5)	
Medicare	17 (53.1)	15 (45.5)	
Current smoker, n (%)	4 (12.5)	2 (6.1)	.43
Parity n	2.4 ± 1.1	2.6 ± 0.9	.30
Previous vaginal deliveries, n	2.3 ± 1.2	2.5 ± 0.8	.28
Hysterectomy, n (%)	14 (43.8)	12 (36.4)	.54
Previous surgery for prolapse, n (%)	4 (12.5)	0	.053
Previous surgery for incontinence, n (%)	2 (6.3)	1 (3.0)	.61
Body mass index, kg/m^2	27.4 ± 5.1	27.8 ± 6.4	.71
Body mass index ≥30 kg/m^2, n (%)	8 (25.0)	9 (27.3)	.84
Pelvic organ prolapse–quantification stage, n (%)			.51
II	7 (21.9)	4 (12.1)	
III	20 (62.5)	24 (72.7)	
IV	5 (15.6)	5 (15.2)	
Pelvic organ prolapse–quantification measurements, cm[c]			
Ba	3.0 (0.0–13.5)	4.0 (−0.5 to 9.0)	.29
Bp	−1.0 (−3.0 to 13.5)	−1.0 (−3.0 to 8.0)	.75
C	−0.8 (−7.5 to13.5)	2.0 (−8.0 to 9.0)	.26
GH	5.0 (2.0–8.0)	5.0 (2.5–8.0)	.27
PB	4.0 (2.0–5.0)	3.5 (1.0–5.5)	.15
Total vaginal length	9.0 (6.5–13.5)	9.0 (7.0–11.5)	.50

The χ^2 test of association was used to compare the groups with respect to percentages; the Mann-Whitney test was used to compare the groups with respect to noncategoric variables.

[a] Data are given as mean ± SD; [b] Based on white and African American groups only; [c] Data are given as median (range).

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need to trim the excess vagina, the surgeon divided the mesh potentially to decrease the risk of exposure at the apex. This woman was in the hysterectomy group and had a postoperative stage 4 prolapse at point C at 2.1 months after a total Prolift. A summary of overall objective anatomic outcomes and global impressions of improvement and severity at a mean follow-up time of 14.3 months (Table 2).

In the mesh group, there was no association between the site of mesh placement and the site of recurrence (Table 3). For patients with recurrences, no statistically significant differences were found between the mesh and no-mesh groups with respect to the percentages with anterior, posterior, or apical recurrences ($P = .44$-$.53$). Three patients in the mesh group had reoperations for prolapse (2 sacral colpopexies and 1 iliococcygeal suspension) vs no reoperations in the no-mesh group ($P = .11$).

Patient satisfaction and QOL

The mesh group had significantly lower overall preoperative distress that was indicated by lower preoperative Pelvic Organ Prolapse Distress Inventory -6 scores than the no-mesh group (Table 4). Postoperative subjective QOL measurements showed statistically significant improvements from baseline for both the mesh and no-mesh groups for almost all QOL measurements and did not differ between the 2 groups 1 year after the procedure (Table 4). Patients in both groups had high subjective satisfaction at 1 year after the procedure, with no statistically significant difference between the mesh and no-mesh groups ($P = .44$). Subjective cure of bulge symptoms was reported by 25 of mesh subjects (96.2)% and 30 of no-mesh subjects (90.9%) at 12 months ($P = .62$).

Colorectal function

Colorectal function that was based on Colorectal Anal Distress Inventory–8 and Colorectal Anal Impact Questionnaire–7 scores was similar before the procedure between the mesh and no-mesh groups and improved significantly in both groups 12 months after the procedure. No significant difference was found between groups with regards to

colorectal function 12 months after the procedure (Table 4).

Sexual function

Sexual function based on the Prolapse and Incontinence Sexual Questionnaire scores was similar before the procedure between mesh and no-mesh groups and improved significantly in both groups 12 months after the procedure. No significant difference was found between groups with regards to sexual function 12 months after the procedure (Table 4).

Vaginal caliber

Preoperative vaginal diameter (median, 7.6 cm [range, 5.7–8.9 cm] vs 7.6 cm [range, 6.4–8.9 cm]; $P = .15$) and vaginal volume (median, 384.8 cm^3 [range, 204.1–684.3 cm^3] vs 408.3 cm^3 [range, 257.4–622.2 cm^3]; $P = .26$) were similar between the mesh and no-mesh groups. Patients with previous hysterectomy had significantly lower preoperative vaginal diameter (median, 7.3 cm [range, 5.7–8.9 cm] vs 7.6 cm [range, 6.4–8.9 cm]; $P = .027$) and volume (median, 346.4 cm^3 [range, 204.1–612.4 cm^3] vs 408.3 cm^3 [range, 257.4–684.3 cm]; $P = .005$) than did those without previous hysterectomy. At 1 year, both the mesh and no-mesh groups had statistically significant decreases in postoperative vaginal diameter (mesh group: median, 7.6 cm [range, 5.7–8.9 cm] vs 6.1 cm [range, 5.7–7.0 cm]; $P < .001$; no-mesh group: median, 7.6 cm [range, 6.4–8.9 cm] vs 6.4 cm [range, 5.17.0 cm]; $P < .001$), vaginal volume (mesh group: 384.8 cm^3 [range, 204.1–684.3 cm^3] vs 214.7 cm^3 [range, 153.1–321.7 cm^3]; $P < .001$; no-mesh group: 408.3 cm^3 [range, 257.4–622.2 cm^3] vs 257.4 cm^3 [range, 127.6–384.8 cm^3]; $P < .001$), and total vaginal length (mesh group: median, 9.0 cm [range, 6.5–11.0 cm] vs 8.0 cm [range, 6.0–10.0 cm]; $P < .001$; no-mesh group: median, 9.0 cm [range, 7.0–11.5 cm] vs 8.0 cm [range, 5.0–10.0 cm]; $P < .001$) compared with preoperative values, but no statistically significant differences were found between the mesh and no-mesh groups ($P = .25$-$.40$).

Complications

Two cystotomies occurred in the mesh group, 1 during dissection and 1 during trocar insertion. Both subjects with cystotomies had previous hysterectomies; the cystotomies were repaired, and mesh was placed without complication or subsequent postoperative sequelae. No serious adverse events that were related to surgery occurred in either group. One subject in each group had a febrile illness while hospitalized. One subject in the mesh group with concurrent hysterectomy received a postoperative blood transfusion. No significant differences

TABLE 2
Anatomic outcomes and quality of life evaluation 12 months after surgery

Variable	Mesh	No mesh	*P* value
National Institutes of Health optimal prolapse by POP-Q stage ≤1: mesh, 32; no mesh, 33, n (%)	12 (37.5)	10 (30.3)	.45
Prolapse by symptoms (bulge): mesh, 26; no mesh, 33, n (%)[a,b]	1 (3.8)	3 (9.1)	.62
Recurrent prolapse: mesh, 20; no mesh, 23, n (%)			> .99
At or above hymen	15 (75.0)	18 (78.3)	
Beyond hymen	5 (25.0)	5 (21.7)	
Reoperation for prolapse: mesh, 32; no mesh, 33, n (%)	3 (9.4)	0	.11
Total reoperation for prolapse or mesh erosion: mesh, 32; no mesh, 33, n (%)	5 (15.6)	0	.017
Point Ba value after operation, cm[b,c]	–1.5 (–3.0 to 0.5)	–1.0 (–3.0 to 1.0)	.077
Point Bp value after operation, cm[b,c]	–2.5 (–3.0 to 0.0)	–3.0 (–3.0 to 0.0)	.27
Point C value after operation, cm[b,c]	–6.0 (–9.0 to –4.5)	–6.5 (–9.0 to –5.0)	.088
TVL: mesh, 27; no mesh, 33[b,c] (mesh, 27; no mesh, 33)	8.0 (6.0–10.0)	8.0 (5.0–10.0)	.35
Patient global impression of improvement: mesh, 26; no mesh, n (%)[b]			0.44
Very much better	16 (61.5)	23 (69.7)	
Much better	6 (23.1)	8 (24.2)	
A little better	0	0	
No change	2 (7.7)	0	
A little worse	1 (3.8)	1 (3.0)	
Much worse	1 (3.8)	0	
Very much worse	0	1 (3.0)	
Patient global impression of severity: mesh, 26; no mesh, 33, n (%)[b]			.71
Normal	18 (69.2)	24 (72.7)	
Mild	6 (23.1)	8 (24.2)	
Moderate	1 (3.8)	0	
Severe	1 (3.8)	1 (3.0)	

The χ^2 test of association was used to compare the groups with respect to percentages; the Mann-Whitney test was used to compare the groups with respect to non-categorical variables.
TVL, total vaginal length.

[a] Bulging sensation present by Pelvic Floor Distress Inventory, item 3; [b] Patients who underwent reoperation for prolapse were excluded from analysis; [c] Data are given as median (range).

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TABLE 3
Mesh placement site vs recurrence site (n = 20)

	Recurrence site, n (%)			
Placement site	Anterior only	Posterior only	Anterior and posterior	Anterior, posterior, and apical
Anterior only	9 (64.3)	4 (28.6)	1 (7.1)	0
Anterior and posterior (total)	4 (66.7)	1 (16.7)	0	1 (16.7)

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were found between the mesh and no-mesh groups with respect to estimated blood loss, preoperative or postoperative hematocrit level, hospital length of stay (Mann-Whitney test, $P = .082$ to 1.0), or 2-week urinary tract infection rate (Fisher's exact test, $P = .20$ to .59). One patient experienced fluctuance and induration at a mesh trocar site 11.5 weeks after anterior Prolift. Incision and drainage were performed in the office, and the patient was treated with Augmentin for 10 days with complete symptom resolution. Abscess cultures were negative.

Of the 32 mesh subjects, 5 women (15.6%) had mesh exposures. One exposure occurred in the concurrent hysterectomy group, and 4 exposures occurred in the previous hysterectomy/vault prolapse group; however, this did not reach statistical significance (log-rank test, $P = .080$). Exposures occurred at 2 weeks, 6 weeks (2 subjects), 7.5 weeks, and 2.1 months and were located along incision lines in the anterior compartment in 3 cases and posterior compartment in 2 cases. Exposures were noted only with Prolift mesh and not with sling mesh. Three of the 5 exposures required additional procedures in the operating room to remove the mesh (Table 5). All exposures resolved after outpatient trimming, without further exposures in these patients. Two exposures were found at the 6-week postoperative visit; 1 of these exposures was trimmed in the office, and the other was asymptomatic and not treated. Both exposures persisted but were asymptomatic at the 1-year visit. During the second interim analysis (when two-thirds of patients reached the 3-month mark), the Data Safety Monitoring Board notified the investigators that the mesh exposure rate had surpassed the predetermined stopping criteria of 15%, and further enrollment in the trial was halted.

Of the 33 no-mesh participants, 5 women (15%) had apical Gore-tex suture exposures; 2 women complained of vaginal discharge and required suture removal in the office at 6 and 9 months after the procedure. One asymptomatic suture Gore-tex suture exposure was noted at 6 months, and another was noted at 12 months; neither exposures required intervention. Another participant had a mild pink discharge and was found to have suture exposure at 16.5 months. However, she was not bothered and chose not to have the suture removed.

No statistically significant differences were found between the mesh and no-mesh groups with respect to long-term complications. De novo stress urinary incontinence developed in 4 of 13 women (30.8%) in the mesh group vs 3 of 19 women (15.8%) in the no-mesh group ($P = .40$). One patient in the mesh group underwent a sling procedure for stress urinary incontinence after the initial prolapse repair (Table 5). No statistically significant differences were found between the mesh and no-mesh groups with respect to new-onset dyspareunia (mesh group, 1/11 women [9.1%] vs no-mesh group, 3/14 women [21.4%]; $P = .60$). The number of participants whose condition required reoperation for recurrent prolapse or mesh exposure was significantly higher in the mesh group: 5 women (15.6%; 3 reoperations for prolapse, 3 reoperations for exposure, with 1 patient having surgery for both prolapse and exposure) vs none in the no-mesh group ($P = .017$). Table 5 details reoperations for exposures and prolapse recurrence.

Two patients died of causes that were unrelated to prolapse repair during the study period. One participant in the mesh group died of myocardial infarction 12 months after surgery (but before her 12-month follow-up visit) and was censored from the 1-year analysis. Another participant in the no-mesh group died 15 months after the procedure after experiencing complications that were related to a diverticular abscess with sepsis.

COMMENT

The key finding of our study was that significant objective and subjective improvements were seen after prolapse repair with or without interpositional mesh. However, mesh was associated with a higher overall reoperation rate and resulted in a >15% risk of exposure.

Strengths and weaknesses of this study have been reported previously.[12] The major strength of this trial is its double-blind, multicenter RCT design. Although mesh kits were provided by the company to maintain patient masking, this study was not industry funded and had excellent follow-up evaluation. Findings of this study should be generalizable to other fellowship-trained pelvic reconstructive surgeons.

The major weakness of this trial was a lack of statistical power for efficacy outcomes because of premature stopping as a result of reaching predetermined mesh exposure rates of >15%. Additionally, some of the complication outcomes may have been "inevitable" because complications resulted in termination of the study. Another potential weakness is the differential follow up between groups. A shorter follow-up period did give the mesh group a slight advantage, because women in this group had less time to have recurrences. Finally, the relatively small number of patients who were available and who consented to participate could call into question the surgical experience of the investigators with mesh. However, our trial was conducted by fellowship-trained surgeons with expertise in all routes of reconstructive pelvic surgery that represent the skilled surgeons to whom new technology often is marketed. All surgeons are in high volume institutions with American Board of Obstetrics and Gynecology/American

TABLE 4
Health-related quality of life variables[a]

Variable	Before the operation		12 mo after the operation		*P* value			
					Within groups		Between groups	
	Mesh	No mesh	Mesh	No mesh	Mesh	No mesh	Before the operation	12 mo after the operation
Pelvic Floor Distress Inventory–20[b]	100.0 (0, 235.4) (n = 32)	140.6 (16.7, 284.4) (n = 33)	29.6 (0, 97.9) (n = 26)	29.2 (0, 255.2) (n = 33)	< .001 (n = 26)	< .001 (n = 33)	.084 (n = 65)	.66 (n = 59)
Pelvic Organ Prolapse Distress Inventory–6	43.8 (0, 91.7) (n = 32)	58.3 (16.7, 100) (n = 33)	0.0 (0, 29.2) (n = 26)	0 (0, 75.0) (n = 33)	< .001 (n = 26)	< .001 (n = 33)	.021 (n = 65)	.79 (n = 59)
Colorectal Anal Distress Inventory–8	14.1 (0, 75.0) (n = 32)	34.4 (0, 84.4) (n = 33)	10.4 (0, 56.3) (n = 26)	12.5 (0, 96.9) (n = 33)	.074 (n = 26)	.028 (n = 33)	.15 (n = 65)	.64 (n = 59)
Urogenital Distress Inventory–6	37.5 (0, 100) (n = 32)	45.8 (0, 100) (n = 33)	8.3 (0, 50.0) (n = 26)	12.5 (0, 83.3) (n = 33)	.002 (n = 26)	< .001 (n = 33)	.58 (n = 65)	.71 (n = 59)
Pelvic Floor Impact Questionnaire–7[b]	23.8 (0, 285.7) (n = 32)	38.1 (0, 233.3) (n = 32)	2.4 (0, 90.5) (n = 26)	0 (0, 157.1) (n = 33)	.002 (n = 26)	< .001 (n = 32)	.81 (n = 64)	.70 (n = 59)
Pelvic Organ Prolapse Impact Questionnaire–7	2.4 (0, 95.2) (n = 32)	9.5 (0, 100) (n = 32)	0.0 (0, 9.7) (n = 26)	0 (0, 19.1) (n = 33)	.021 (n = 26)	< .001 (n = 32)	.48 (n = 64)	.10 (n = 59)
Colorectal Anal Impact Questionnaire–7	4.8 (0, 95.2) (n = 32)	4.8 (0, 85.7) (n = 33)	0.0 (0, 23.7) (n = 26)	0 (0, 66.7) (n = 33)	.008 (n = 26)	.039 (n = 33)	.89 (n = 65)	.97 (n = 59)
Urinary Impact Questionnaire–7	14.3 (0, 100) (n = 32)	19.0 (0, 100) (n = 33)	0.0 (0, 90.5) (n = 26)	0 (0, 85.7) (n = 33)	.007 (n = 26)	< .001 (n = 33)	.98 (n = 65)	.53 (n = 59)
Prolapse and Incontinence Sexual Questionnaire–12[c]	31.0 (19.0, 43.6) (n = 17)	32.0 (16.0, 42.0) (n = 17)	34.0 (27.0, 43.0) (n = 15)	35.0 (29.0, 45.0) (n = 16)	.007 (n = 13)	.002 (n = 16)	> .99 (n = 34)	.66 (n = 31)
Dyspareunia, n (%)[d]	3 (17.6) (n = 17)	3 (16.7) (n = 18)	1 (6.7) (n = 15)	3 (18.8) (n = 16)	> .99 (n = 13)	> .99 (n = 16)	> .99 (n = 35)	.60 (n = 31)

The χ^2 test of association was used to compare mesh and no-mesh groups with respect to percentages; the Mann-Whitney test was used to compare mesh and no-mesh groups with respect to noncategoric variables. Within each group, the McNemar test was performed to compare preoperative and postoperative percentages; the Friedman test was performed to compare preoperative and postoperative noncategoric variables.

[a] Patients who underwent reoperation for prolapse were excluded from the 12-month analyses; [b] Lower scores represent better outcome; [c] Higher scores represent better outcome; [d] Prolapse and Incontinence Sexual Questionnaire, item 5, response = usually or always.

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Board of Urology accredited fellowship programs.

To date, 3 RCTs have been conducted that have evaluated mesh for vaginal prolapse repair in the anterior compartment only. Hiltunen et al[4] reported a higher cure rate for anterior repair with polypropylene mesh overlay at 1 year, but with a 17% exposure rate. This is consistent the 15.6% mesh exposure rate that halted our trial.[12] The trial of Hiltunen et al excluded women with apical prolapse that required treatment or those with primarily posterior prolapse; our study included women with stage ≥2 prolapse in any compartment. The second RCT used blinded examiners, like our trial, and showed a cure rate of 55% for anterior repair vs 87% for Perigee (American Medical Systems, Minnetonka, MN) at 1 year.[5] One potential limitation of their study, however, was its support by an educational grant from the company that makes the mesh that was used in the trial.

Recently, Altman et al[20] randomly assigned 200 women to Prolift and 189 women to traditional colporrhaphy at 53 Nordic hospitals. Their trial found a significantly higher cure rate for the anterior compartment in the mesh group (60.8% vs 34.5%). Similar to our trial, they found more complications in the mesh group. Their trial had some important differences from ours. First, ours was a multicompartment mesh RCT; theirs was anterior only. Also, only a small percentage of their patients had clinically significant apical prolapse, whereas the median stage of apical prolapse in our trial was stage 2-3. Additionally, examiners in their trial were not masked to the treatment group.

Two trials evaluated mesh use for multicompartment defects. One trial found no difference between traditional colporrhaphy and polypropylene mesh overlay for combined anterior and posterior prolapse at 1 year.[21] However, women were excluded if prolapse was present only in the anterior or posterior compartment or if apical prolapse was present beyond the hymen. Our trial included women with stage ≥2 prolapse in any compartment. More recently, Withagen et al[22] performed a multicenter RCT at 13 sites that compared Prolift to conventional vagi-

TABLE 5
Reoperations for erosions and prolapse recurrence

Patient	Initial surgery	Indication for reoperation	Extrusion/exposure or recurrence site	Surgery	Reoperation time
1[a]	Total Prolift, partial vaginectomy of excess 14-cm vagina	Extrusion, 2 cm	Posterior	Excision of mesh	10 wk
		Prolapse	Stage 4 apical, anterior, posterior	Abdominal sacral colpopexy	9.8 mo
2	Total Prolift	Extrusion, 1 × 2 cm	Posterior	Excision of mesh	4 mo
3[b]	Anterior Prolift, transobturator sling	Persistent voiding dysfunction, prolapse	Stage 2 posterior, stage 1 apical, enterocele	Sling revision, iliococcygeal suspension	4.6 mo
4	Anterior Prolift	Prolapse	Stage 3 posterior, enterocele	Robotic sacral colpopexy	10 mo
5[c]	Anterior Prolift	Exposure, 5-mm; worsened stress urinary incontinence symptoms	Anterior	Excision of mesh, retropubic sling	10 mo

Prolift; Ethicon Women's Health and Urology, Somerville, NJ.

[a] Anterior recurrence was noted at 8 weeks, with stage 4 recurrence at 9.5 months; [b] Transobturator sling procedure was performed for stress urinary incontinence with preoperative diagnosis of detrusor hypoactivity and Valsalva voiding; prolapse recurrence that was noted intraoperatively was fixed at the time of sling release because of the belief that recurrent prolapse was contributing to voiding dysfunction; [c] Interval collagen was planned if mild preoperative stress urinary incontinence symptoms worsened; the patient had 1 week of improvement after collagen and sling procedure was then performed for definitive stress urinary incontinence cure.

Sokol. RCT of mesh for prolapse repair. Am J Obstet Gynecol 2012.

nal prolapse repair. Although their study showed higher cure rates in the treated compartment in the mesh group, examiners were unblinded. Despite unblinded examiners, they reported failure rates of 66% in the conventional group and 49% in the mesh group when failure was defined as overall pelvic organ prolapse as stage ≥2. As in our double-blind trial, these failure rates are higher than reported elsewhere in the literature. Moreover, they reported an exposure rate of 16.9% at 1 year, which is consistent with our exposure rate of 15.6%. In their trial, 22 different surgeons were involved, with some contributing as few as a single subject to the study. Although this may have resulted in higher failure and exposure rates in their trials, it may more closely represent "real world" experience, where some surgeons perform these repairs infrequently.

Our relatively low objective cure rate may be due to a number of factors. First, we used stringent objective outcome criteria. Despite our high objective "failure" rate, most participants were happy with their repair, had improved QOL, and were not symptomatic of recurrent prolapse. Indeed, >75% of objective recurrences occurred proximal to the hymen, and prolapse above the hymen is rarely symptomatic.[23,24] Second, investigators who were masked to the procedure performed postoperative examinations, which reduced the risk of surgeon bias. As we previously reported,[12] cure rates for synthetic mesh procedures have been reported to be as low as 43.7% for stage <2 when blinded examinations are performed.[25] One recent RCT that compared laparoscopic sacral colpopexy to total Prolift for prolapse after hysterectomy found a 77% cure rate at 2 years in the laparoscopy group vs 43% in the vaginal mesh group ($P = .006$).[26] Similar to our trial, examiners were blinded to treatment allocation, and cure rates for vaginal prolapse repair were lower than reported in non-RCTs. Third, we had excellent (92.3%) follow-up evaluations at 1 year. This is higher than many of the studies with >1-year follow up. Twenty-four to 40% loss to follow-up rates in these studies[9,27] may have changed their reported cure rates greatly. We do agree with Jacquetin et al[28] that shortcomings of the POP-Q may explain some of the anatomic "failures" after prolapse repair because the POP-Q cannot differentiate between distal anterior prolapse (ie, ureterocele) and more clinically relevant mid-vaginal prolapse. As stated by Barber et al,[29] "the definition of success substantially affects treatment success rates after pelvic organ prolapse surgery. The absence of vaginal bulge symptoms postoperatively has a significant relationship with a patient's assessment of overall improvement, although anatomic success alone does not."

Despite a significantly shorter follow-time in the mesh group, our study found a significantly higher reoperation rate in participants who received mesh. This is consistent with a systematic review by Diwadkar et al,[30] who reported that the total reoperation rate was highest with vaginal mesh kits compared with procedures that were performed vaginally and abdominally.[30]

High-quality RCTs are necessary to inform clinical decisions regarding mesh use in pelvic reconstructive surgery. A lack of high-quality evidence persists, despite the widespread use of vaginal mesh procedures. Clinical practice guidelines regarding mesh use that have been published by the Society of Gynecologic Surgeons could not make recommendations about the use of synthetic graft for multiple compartment disease because of a lack of comparative studies on which to base recommendations.[31]

Lighter meshes and trocar-less delivery systems likely will decrease complications that are associated with vaginal

mesh use. Nonetheless, properly designed clinical trials are necessary to evaluate whether synthetic mesh confers benefit for vaginal prolapse repair. Based on the results of this study and the high exposure rates that have been noted in other studies, risks may outweigh benefits for the older trocar-based mesh systems, even when fellowship-trained pelvic reconstructive surgeons perform these procedures. ■

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EXHIBIT FF

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ORIGINAL ARTICLE

Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials: a systematic review

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Abstract
Introduction and hypothesis This study describes the incidence, risk factors, and treatments of graft erosion, wound granulation, and dyspareunia as adverse events following vaginal repair of pelvic organ prolapse with non-absorbable synthetic and biologic graft materials.
Methods A systematic review in Medline of reports published between 1950 and November 2010 on adverse events after vaginal prolapse repairs using graft materials was carried out.
Results One hundred ten studies reported on erosions with an overall rate, by meta-analysis, of 10.3%, (95% CI, 9.7 – 10.9%; range, 0 – 29.7%; synthetic, 10.3%; biological, 10.1%). Sixteen studies reported on wound granulation for a rate of 7.8%, (95% CI, 6.4 – 9.5%; range, 0 – 19.1%; synthetic, 6.8%; biological, 9.1%). Dyspareunia was described in 70 studies for a rate of 9.1%, (95% CI, 8.2 – 10.0%; range, 0 – 66.7%; synthetic, 8.9%; biological, 9.6%).
Conclusions Erosions, wound granulation, and dyspareunia may occur after vaginal prolapse repair with graft materials, though rates vary widely across studies.

Keyword Pelvic organ prolapse · Erosion · Dyspareunia · Granulation

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Introduction

Pelvic organ prolapse (POP) affects up to one third of women [1]. Approximately 200,000 women undergo surgical correction of POP in the USA annually, and 29% of all procedures are repeat operations [2]. High recurrence rates of POP have led surgeons to seek more durable surgical interventions with the use of graft material to augment prolapse repairs. The Society of Gynecologic Surgeons (SGS) formed a Systematic Review Group to provide up-to-date systematic reviews and practice guidelines on important gynecological surgery topics. The first topic chosen was the use of graft materials in the transvaginal repair of POP. We have previously reported the findings of the systematic review and published the guidelines for use of graft materials in vaginal prolapse repair [3].

In the systematic review, several adverse events directly attributable to the use of graft material were identified including graft erosion, granulation tissue formation, and

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dyspareunia/vaginal pain [3]. This is a more detailed report of these three adverse events. Our objectives were to identify and characterize the incidence, risk factors, and treatment of these adverse events after repair with synthetic and biological grafts.

Materials and methods

A systematic review of all vaginal prolapse repair papers using graft materials published between 1950 and November 2007 was conducted by the Systematic Review Group of the Society of Gynecologic Surgeons. Studies were identified from a Medline search identifying terms including "vaginal or uterine prolapse," "rectocele," "cystocele," "surgery of the pelvic floor," "surgical mesh," "vagina," "rectum," and "bladder". We included studies published in any language that reported anatomical, symptomatic, or adverse event outcomes on any type of graft material in transvaginal pelvic organ prolapse repairs (excluding abdominal or laparoscopic graft use). Details regarding the search strategy employed and results have been previously published [3].

For the present study, we conducted a systematic review of the adverse events of graft erosion, wound granulation, and dyspareunia reported in all comparative studies or case series with at least 30 subjects in the graft arm, with no language restriction. Some of these studies were previously identified in the SGS systematic review, and that search was updated to include additional studies published between November 2007 and November 2010. All studies were reviewed for additional details regarding timing of diagnosis of the complication as related to the incident surgery in weeks, potential risk factors for the complication as outlined by the author, diagnostic approach including radiological evaluation and details reported regarding management. The original data extraction, performed for the full systematic review [3], was done by a single investigator and checked by at least one additional investigator. Additional data for this review were extracted by four investigators (HA, DDR, LL, and JLC) with each paper reviewed twice to assure accuracy of the data extraction. We defined graft erosion as exposed graft material in the vagina or surrounding pelvic organs. For graft erosion treatment, we specifically captured details about the use of vaginal agents and the need for additional surgeries or procedures. In addition, we captured whether the procedure to remove the graft was performed in the office or operating room. Granulation tissue was defined as the formation of granulation tissue at the site of graft placement, and we included all reported cases of de novo dyspareunia; otherwise, we reported on persistent dyspareunia after surgery.

We performed meta-analyses of the adverse event rates of cohorts of women receiving the same graft material using the DerSimonian and Laird random effects model [4]. Meta-analyses were restricted to the two most commonly used graft materials (non-absorbable synthetic and biological graft). Since most studies evaluated adverse event rates in cohorts of women all receiving the same graft material (as opposed to comparative studies), we performed indirect comparisons across studies of adverse event rates. We compared the summary adverse event rates of studies using the two graft materials with t tests. Statistical heterogeneity, a measure of whether differences in reported effects were due to chance, was tested with the Q statistic (significant when $p < 0.10$) and quantified its extent with I [2, 5]. Since this study was a systematic review, it was exempted from human research review committee approval.

Results

The initial Medline search identified 2,260 citations. After abstract screening, 196 full text articles were assessed in detail; 74 papers described the use of vaginal graft materials for the repair of POP. Of these, 58 studies reported on any adverse events, 49 of which (66% of all graft articles) included specific information regarding graft erosions, wound granulation, or dyspareunia. We updated that search to include additional studies published between November 2007 and November 2010. There were another 1,269 citations, and we identified 101 additional papers describing the use of vaginal graft material with at least 30 subjects in the mesh arm. From these papers, 77 additional studies reported on these adverse events.

Graft erosion

Graft erosion was documented in 110 studies after excluding one study that reported only summary adverse event rates across a variety of different graft materials [6] and two studies that used absorbable synthetic graft (polyglactin-10) [7, 8]. The 110 studies included 11,785 women and had a summary incidence of 10.3% (95% CI, 9.7 – 10.9%; range, 0 – 29.7%; Table 1, Figs. 1 and 2). The studies were statistically heterogeneous in their graft erosion rates. We evaluated study-level differences such as graft type, publication year, and sample size, and none of these factors adequately explained the heterogeneity among the studies. Similar erosion rates occurred after use of synthetic (10.3%, 91 studies, N = 10,440) and biological grafts (10.1%, 19 studies, N = 1,345). The reported timing of diagnosis of graft erosion ranged from 6 weeks to 12 months.

Table 1 Comparison of rates of adverse events between non-absorbable synthetic and biological graft

Adverse event graft type	Number of studies	Total number of adverse events/total number of patients	Summary adverse event rate[a] (95% confidence interval) (%)	*P* difference (subgroups)
Graft erosion				
All grafts	110	982/11,785	10.3 (9.7, 10.9)	
Non-absorbable synthetic	91	897/10,440	10.3 (9.7, 11.0)	NS
Biologic	19	85/1,345	10.1 (8.3, 12.3)	
Wound granulation tissue formation				
All grafts	16	92/1,762	7.8 (6.4, 9.5)	
Non-absorbable synthetic	9	49/1,113	6.8 (5.2, 8.9)	NS
Biologic	7	43/649	9.1 (6.8, 12.1)	
Dyspareunia				
All grafts	70	350/5,638	9.1 (8.2, 10.0)	
Non-absorbable synthetic	54	284/4,566	8.9 (8.0, 10.0)	NS
Biologic	16	66/1,072	9.6 (7.6, 12.1)	

NS statistically non-significant ($p>0.05$)

[a] Calculated by meta-analysis

Fourteen studies reported on potential risk factors for graft erosion [9–22].The most commonly cited potential risk factors was concomitant hysterectomy, but other potential risk factors included patient age, surgeon experience, the use of inverted "T" colpotomy incisions, smoking, and diabetes mellitus.

Graft erosion symptoms included vaginal discharge, odor, vaginal pain, dyspareunia, or pain experienced by the sexual partner. Management of graft erosions in non-absorbable synthetic graft was reported in 76 studies, involving 795 women: 165 (21%; pooled, not meta-analyzed, estimate) were successfully treated with estrogen or antiseptic agents, 87 (11%) were successfully treated with excision in the surgeon's office, and 448 (56%) were treated with surgical excision in the operating room, with some women requiring two to three additional surgeries to resolve symptoms. Regarding management of erosion in biological graft, this was reported for 35 of 63 (56%) women from 12 studies with half of these patients responding to local treatment with topical agents without the need for surgical revision.

Wound granulation

Wound granulation was reported in 17 papers, including one study that used a variety of different graft materials [7] and was not included in the meta-analysis. The overall incidence of granulation tissue in the remaining 16 studies was 7.8% (95% CI, 6.4 – 9.5%; range, 0 – 39%, N = 1,762; Table 1, Fig. 3). The studies were statistically heterogeneous in their wound granulation rates. No specific factor adequately explained the heterogeneity among studies, and the rate of wound granulation in the seven studies that used biological grafts was higher (9.1%) than in the nine studies of non-absorbable synthetic graft (6.8%), but this difference did not reach statistical significance. One paper reported that wound granulation occurred within 8 weeks of surgery [23], and another paper reported that graft placement with permanent braided sutures was a risk factor for wound granulation [7]. Two papers reported treatment approaches to wound granulation; one paper reported spontaneous resolution [23], and another reported resolution with suture removal and application of silver nitrate [24].

Dyspareunia

Dyspareunia was reported in 71 papers, including one study of absorbable synthetic grafts [8] that was excluded from meta-analysis. The overall incidence in the remaining 70 studies was 9.1% (95% CI, 8.2–10.0%; range, 0 – 66.7%; N = 5,638; Table 1, Figs. 4 and 5). The studies were statistically heterogeneous in their reporting on the incidence of dyspareunia. No specific factor adequately explained the heterogeneity among studies. A similar incidence of dyspareunia occurred after use of synthetic (8.9%, 54 studies) and biological grafts (9.6%, 16 studies). There was a lack of consistency in reporting whether the population analyzed for dyspareunia was restricted to sexually active patients or included entire study populations. Cited risk factors in five papers included posterior repair [10, 11, 24] and mesh erosion [25, 26]. In two papers, treatments included the use of vaginal estrogen cream [10] or excision of mesh erosions [25].

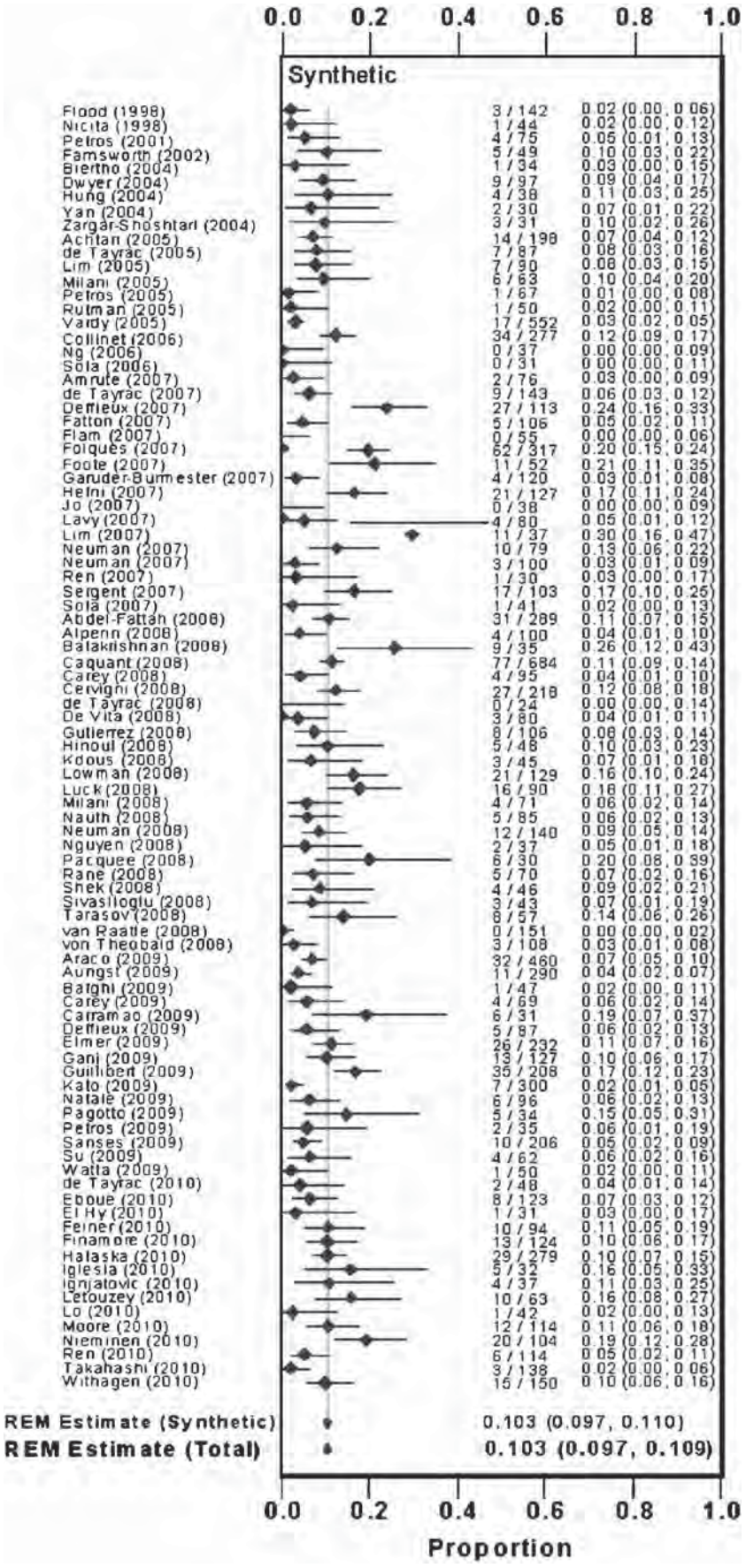

Fig. 1 Rates of graft erosion after non-absorbable synthetic graft. Studies of women receiving non-absorbable synthetic grafts for vaginal prolapse in which adverse event rates were reported. For each study, the proportion and 95% confidence interval of women with the outcome are plotted. The *diamond* indicates the overall proportion of women with the outcome across the studies by random effects model meta-analysis

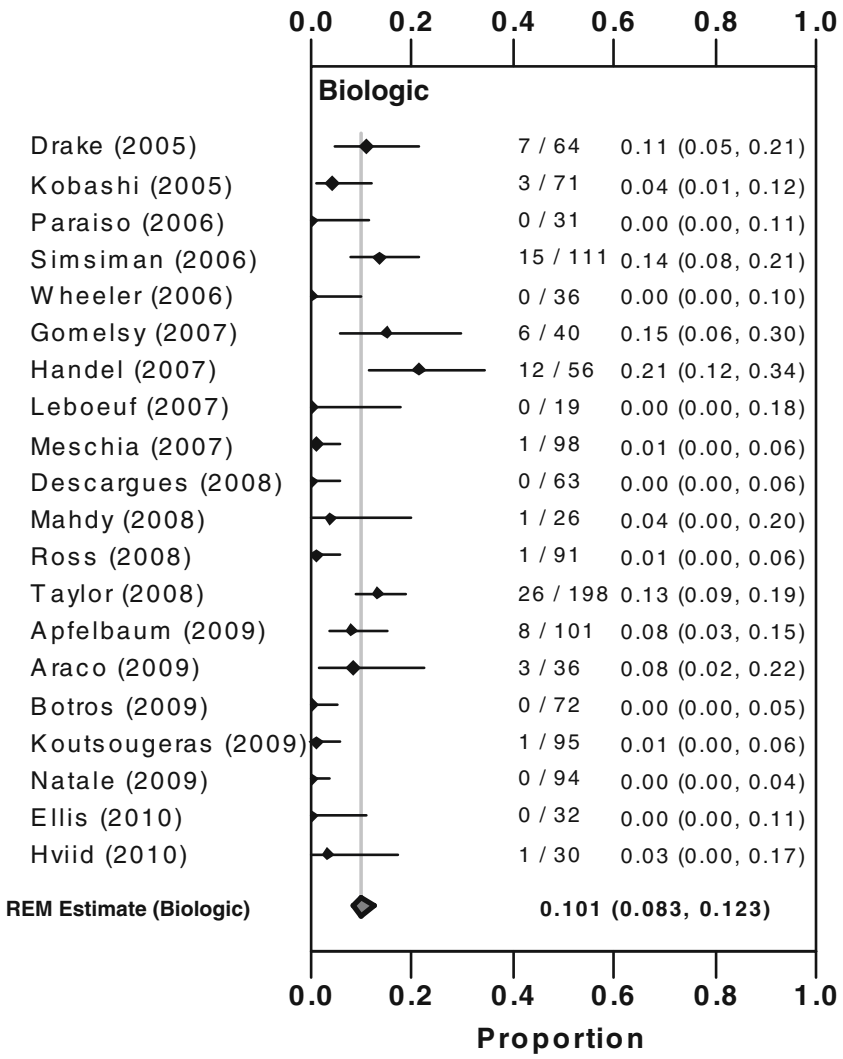

Fig. 2 Rates of graft erosion after biological graft. Studies of women receiving biological grafts for vaginal prolapse in which adverse event rates were reported. For each study, the proportion and 95% confidence interval of women with the outcome are plotted. The *diamond* indicates the overall proportion of women with the outcome across the studies, by random effects model meta-analysis

Discussion

In our original systematic review [3], we reported the anatomical and symptomatic efficacy of treating prolapse using graft augmentation and described the incidences and spectrum of adverse events associated with grafts placed vaginally. In this current analysis, a more detailed accounting is made of three adverse events: graft erosions (10.3%), wound granulation (7.8%), and dyspareunia (9.1%). Reported risk factors and treatment strategies for these three adverse events varied widely.

Similar incidence rates of erosion occurred using synthetic or biological grafts. However, most biological graft erosions were managed conservatively, while synthetic graft erosions often require operative revision. The available data suggest that graft erosions occur within 1 year of surgery and typically present with vaginal discharge, vaginal pain, and/or dyspareunia. However, few more erosions can be detected with longer follow-up, and there is a need to assess patients for graft exposure actively at any time they are evaluated after their surgery. A provider should perform a focused and meticulous examination looking for this graft exposure, as many patients may be asymptomatic or mildly symptomatic but would not correlate their symptoms with this adverse event.

Two factors were repeatedly cited as risks for vaginal graft erosion: increasing patient age and concomitant hysterectomy and/or rectocele repair at the time of vaginal prolapse repair [9–11]. These risks factors are similar to what is known about risk factors for mesh exposure with abdominal or laparoscopic sacrocolpopexy, and many papers are not powered to detect significant differences regarding these risk factors. Many clinicians used vaginal estrogen with or without vaginal antibiotic therapy as an initial treatment for erosions. However, the majority of symptomatic mesh erosions (67%) required surgical excision either in the office or in the operating room.

Granulation tissue formation was reported in 7.8% with a wide range of occurrence across the studies (0 – 39%). This complication was more commonly reported following

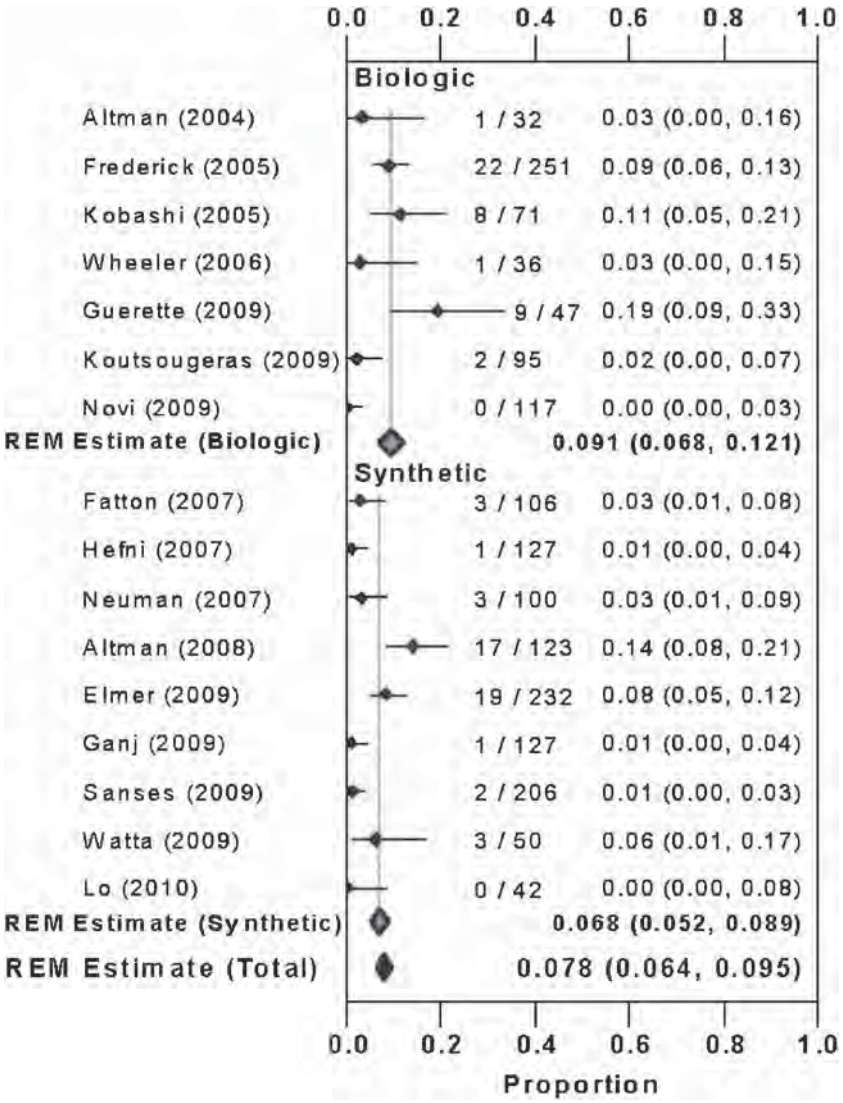

Fig. 3 Rates of wound granulation after biological and non-absorbable synthetic graft. Studies of women receiving grafts for vaginal prolapse in which adverse event rates were reported. For each study, the proportion and 95% confidence interval of women with the outcome are plotted. The *diamond* indicates the overall proportion of women with the outcome across the studies, by random effects model meta-analysis

the use of biological grafts (9.1%) than in synthetic grafts (6.8%), though the difference was not statistically significant. Time to presentation of this granulation tissue formation was not consistently reported but was as little as 8 weeks postoperatively [23]. Most granulation appeared to result from exposed suture material—braided suture, in particular [7]. Some cases resolved spontaneously or after removal of exposed sutures in the office with application of silver nitrate [23, 24].

Studies reporting on dyspareunia following graft use were not consistent in reporting whether these incidence rates of dyspareunia are de novo or persistence of already existing pain. Overall, dyspareunia affected 9.1% of patients, with similar rates between biological and non-absorbable synthetic grafts (9.6% and 8.9%, respectively). However, these may be underestimations of the true dyspareunia rate, since some studies did not explicitly limit their analyses to sexually active women. In the few studies that attempted to identify how dyspareunia presented or possible risk factors for de novo pain, concomitant posterior repair [10, 11, 24] and/or mesh erosion [25–28] were common themes. Of course, dyspareunia may also occur with native tissue prolapse repairs, and it is unknown whether these incidence rates observed after graft augmentation are significantly higher than what would be expected with native tissue repairs.

The strength of this report is that it results from a comprehensive systematic review of the literature with well-defined outcomes; an attempt was made to collect all relevant published papers—with no language restrictions—to identify the spectrum of possible adverse events. The most significant limitation to an analysis of this kind is the body of literature from which it is made. In general, pelvic floor symptoms, sexual, bladder, and bowel dysfunction were poorly reported as were quality of life outcomes. Some studies described no differences in

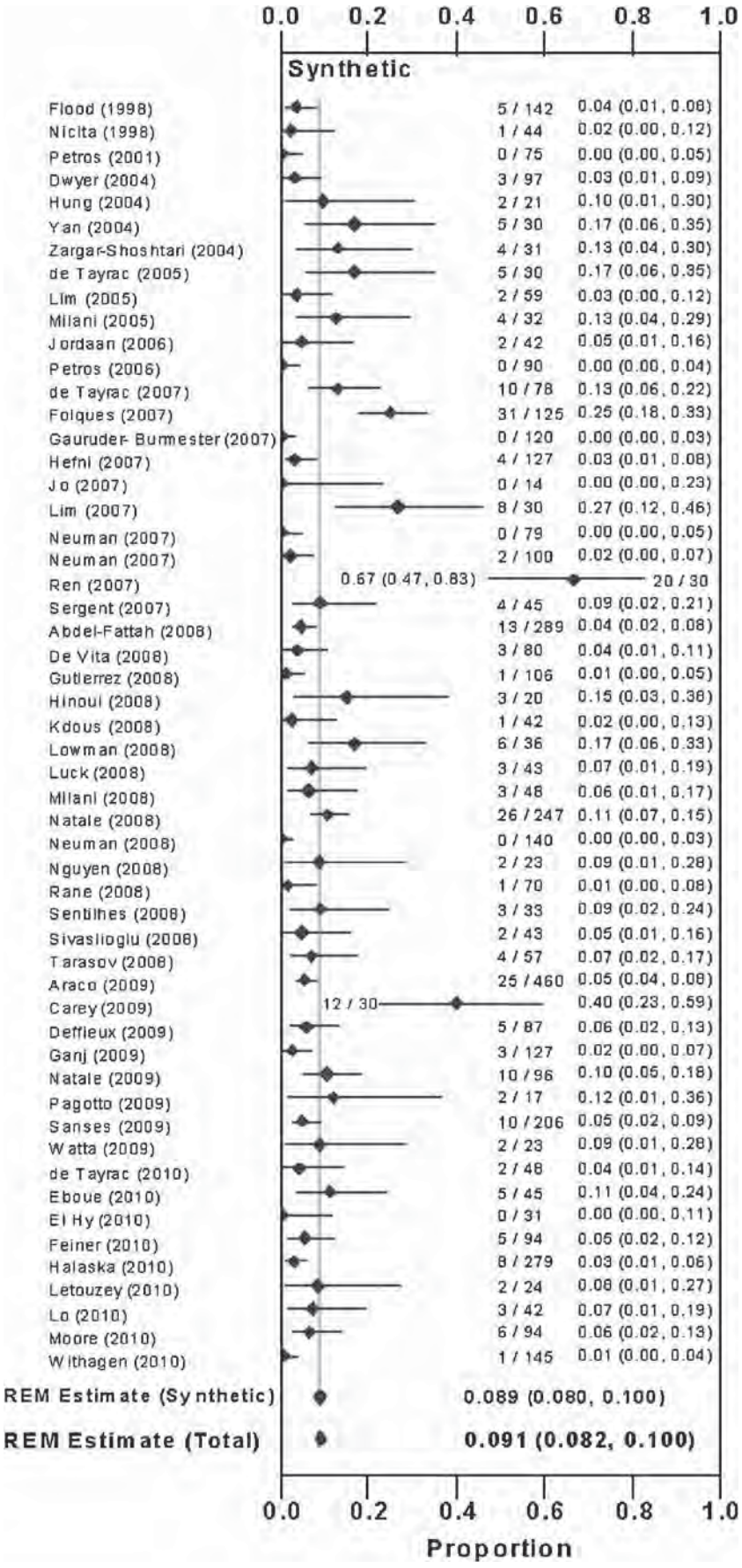

Fig. 4 Rates of dyspareunia after non-absorbable synthetic graft. Studies of women receiving non-absorbable synthetic grafts for vaginal prolapse in which adverse event rates were reported. For each study, the proportion and 95% confidence interval of women with the outcome are plotted. The *diamond* indicates the overall proportion of women with the outcome across the studies, by random effects model meta-analysis

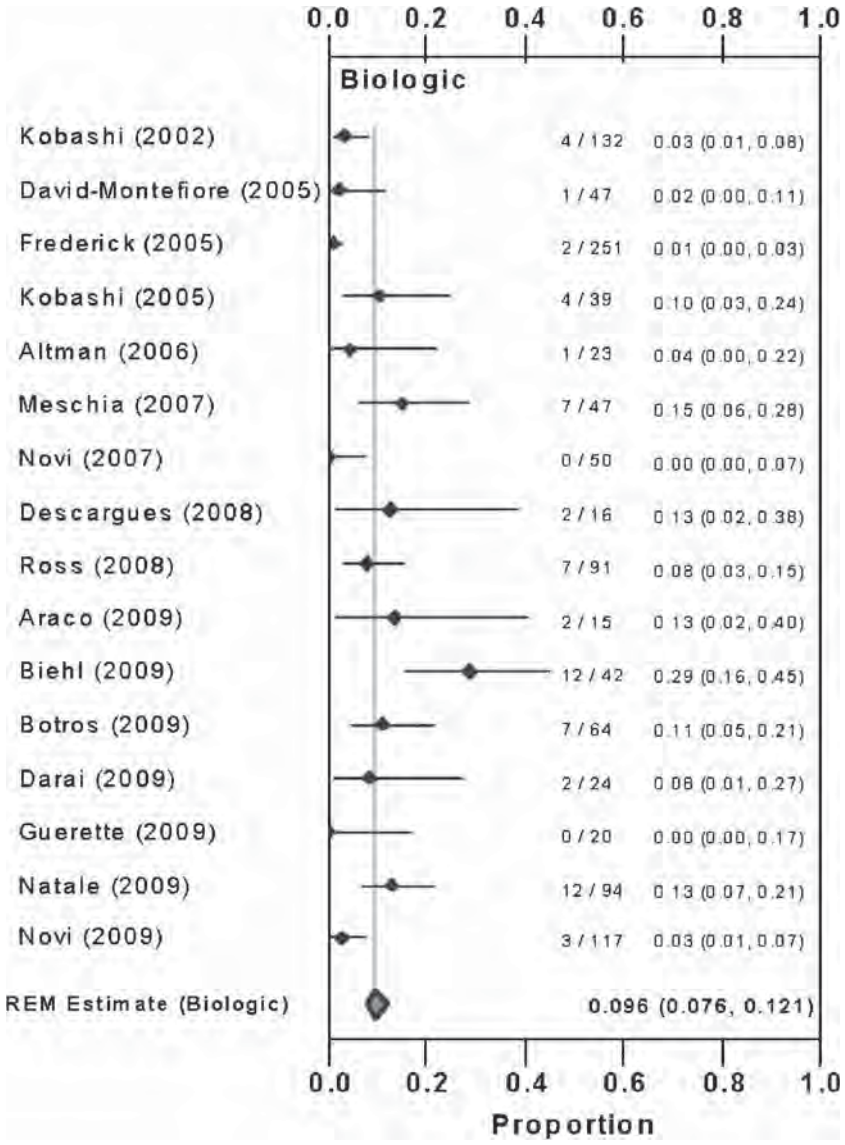

Fig. 5 Rates of dyspareunia after biological graft. Studies of women receiving biological grafts for vaginal prolapse in which adverse event rates were reported. For each study, the proportion and 95% confidence interval of women with the outcome are plotted. The *diamond* indicates the overall proportion of women with the outcome across the studies, by random effects model meta-analysis

functional outcomes (such as dyspareunia) between graft and no-graft treatment arms, but most published studies are underpowered to make such conclusions [3]. Most importantly, none of the studies could directly compare adverse event incidence between synthetic and biological grafts. The indirect comparisons across studies, as performed here, can never fully account for differences in populations, settings, and surgery unrelated to the choice of graft material. Randomized controlled trials of different graft materials are needed to reliably determine relative benefits and harms of the different grafts. Furthermore, it remains a question whether certain subgroups of women may be more likely to benefit from graft use in repairs or whether there are definitive risk factors for graft-related adverse events.

These limitations lead to recommendations for future research examining the benefits and harms of graft augmentation for vaginal prolapse repair. For future randomized or observational studies, validated measures should be used to assess these adverse events at prescribed postoperative intervals. This lack of utilization of quality of life measures was very evident regarding measurement of the impact on sexual function. Most studies did not capture what proportion of women were sexually active, how many had preexisting sexual dysfunction, and how many experienced improvement in function. There was a trend toward improvement in collection of this information in the more recently published studies from the last 2 years, but this will be better assessed as more studies continue using available validated measures such as the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire [29]. Ideally, postoperative follow-up should be > 1 year, as most vaginal erosions appear to be captured within the first year after surgery. Furthermore, when reporting on graft complications, it is advised to follow the recommended terminology

by the joint International Urogynecological Association/ International Continence Society Working Group on Complications Terminology. They recommended abandoning the term "erosion" and replacing with new terms:

Exposure A condition of displaying, revealing, exhibiting or making accessible (e.g., mesh exposure).

Extrusion Passage gradually out of a body structure or tissue.

In addition, better estimates of the frequency of uncommon adverse events will require more complete post-marketing surveillance or registries.

Finally, cystoscopy and rectal exams should be considered at the time of surgery as visceral injuries can occur, and without screening, these adverse events may be missed.

In October 2008, the US Food and Drug Administration (FDA) issued a Public Health Notification of the potential for serious complications associated with transvaginal placement of surgical mesh in repair of POP and stress urinary incontinence [30]. In the preceding 3 years, the FDA had received over 1,000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and stress urinary incontinence. The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia. There were also reports of bowel, bladder, and blood vessel perforation during insertion.

The use of graft augmentation in prolapse repair came as a necessity from the significant failure rates with native tissue repairs. These native tissue repairs may be complicated by dyspareunia and granulation tissue formation in a similar manner to what occurs with graft-augmented repairs. This systematic review should help to further inform physicians on the incidences of these possible complications and should aid in counseling patients when gaining their informed consent for a planned surgical procedure.

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Conflicts of interest None.

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EXHIBIT GG

anatomically reconstruct extensive posterior compartment defects is important for practicing gynecologists and urogynecologists. Education in this, however, is variable amongst postgraduate programs. Results of isolated overlapping anal sphincteroplasty for the management of fecal incontinence are disappointing with complete functional success reported in approximately 60 % of patients and long-term success rates decreasing to 25 % at 10 years. However, younger women who present with extensive obstetric perineal injury and undergo sphincteroplasty in addition to a posterior repair, such as a modification of the Noble-Mengert-Fish operation as described by Veronikos et al., have shown far more promising anatomic (94 %) and functional (90 %) results. In this video, a scripted storyboard was constructed that outlines the key surgical steps of a comprehensive posterior compartment repair which include 1) surgical incision that permits access to posterior compartment and perineal body, 2) dissection of the rectovaginal space up to the level of the cervix, 3) plication of the rectovaginal muscularis, 4) repair of the internal and external anal sphincters, and 5) reconstruction of the perineal body. Using a combination of graphic illustrations and live video footage, tips on repair are highlighted including the use of interrupted subcuticular perineal stitches that have been reported to decrease perineal pain. The goals at the end of repair are to: have improved vaginal caliber allowing two fingerbreadths, increased rectal tone along the entire posterior vaginal wall, have the anus and introitus in the same vertical plane, have the posterior vaginal wall at a perpendicular plane to the perineal body, reform the hymenal ring, and not have an overly elongated perineal body. Conclusion: This video provides a step-by-step guide for how to perform an overlapping sphincteroplasty and posterior repair.

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Long-term Follow-up of the TVT operation: 17 years results

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Objective: To follow-up the performance of the TVT procedure in a very early cohort of women operated on for stress urinary incontinence.
Background: Between 1st of January 1995 and 15th of August 1996 90 consecutive women suffering from stress urinary incontinence were operated on with the Tension-free Vaginal Tape (TVT) method in three Nordic centers: Helsinki, Stockholm and Uppsala. All operated women were primary uncomplicated cases of stress incontinence. The surgical procedure was performed in local anaesthesia as originally described.
Methods: At the 17 years follow-up visit careful attention was paid to possible adverse effects of the tape on tissues by thorough gynecological examination. A cough stress test was performed with a comfortably filled bladder and post-void residual urine volumes (PVR) were measured. Subjective performance was assessed by a VAS, by UDI-6, IIQ-7 and PGII. The women were asked if they leaked on straining and if they would recommend the operation to friend.
Results: Of the initial 90 women 11 were deceased and 5 seriously demented not able to cooperate in any way. Thus 74/90 (82 %) women could potentially be assessed. With 16 women lost to follow-up 58/74 (78.4 %) could be contacted. Twelve women were unable to visit the clinic and therefore evaluated by a telephone interview. Finally 46/74 (62 %) could be assessed at the clinics according to the protocol.. The mean time of follow-up was 16 years and 9 months (range 15 y, 3 m-17y, 9 m). The women's mean age at follow-up was 69 years (range 51–89). A negative stress test was seen in 42/46 (93 %) women. The mean PVR was 48 ml (range 0–550) with 89 % having a PVR less than 100 ml. Fifty three women answered the question on being dry on straining: 42 (79 %) claiming so, while 11 (21 %) women said they leaked. Ninety eight % would recommend the operation to a friend. Favourable scores were recorded in the VAS, UDI-6 and IIQ-7.In the PGII 87 % thought they were cured or significantly better than before the operation. Only one patient had a small protrusion of the tape, with no subjective complaints. Thus 45/46 (98 %) of the women had no sign of any tape problems.
Conclusion: Seventeen years after the TVT operation 62 % of the initial cohort could be assessed at the clinics according to the protocol. No women had adverse reactions or symptoms of the initially implanted tape material. In one women a small protrusion was noted. Of the assessed women 93 % were objectively cured. Subjectively 87 % of the women were cured or significantly better and 98 % would recommend the operation to a friend. The TVT procedure proofs to be safe and effective for at least 17 years.

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A RANDOMIZED COMPARISON OF SINGLE INCISION MID-URETHRAL SLING (MINIARC™) AND TRANSOBTURATOR MID-URETHRAL SLING (MONARC™) IN WOMEN WITH STRESS URINARY INCONTINENCE.

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A randomized comparison of single incision mid-urethral sling (MiniArc™) and transobturator mid-urethral sling (Monarc™) in women with stress urinary incontinence.

Objective: To compare subjective and objective cure, morbidity and discomfort following MiniArc™ and Monarc™ sub-urethral sling in women with stress urinary incontinence.
Background: Mid-urethral sling procedures, such as Monarc™, have become the treatment of choice for women with stress urinary incontinence. Single incision slings, such as MiniArc™, have been introduced to reduce postoperative pain and improve recovery with comparable effectiveness. However, this has never been investigated in a well-powered randomized trial.
Methods: We performed a randomized controlled trial (NTR3783) in two Dutch, two Belgian and one French teaching hospitals. Women with symptomatic stress urinary incontinence were eligible. Women with prior stress urinary incontinence surgery and/or a pelvic prolapse stage ≥2 (ICS) were excluded. Women were randomly allocated to a single incision mid-urethral sling (MUS) (MiniArc™) or transobturator MUS (Monarc™). Surgeons had performed at least ten of each prior to start of inclusion.
Primary outcome was subjective cure at 12 months after surgery defined as responding with 'no' or 'slightly bothered' to the question: 'Are you bothered by urinary incontinence during physical activity like coughing or sneezing?' Co-primary outcome was pain during the first 3 days after surgery, measured using VAS scores.
Secondary outcomes were objective cure (defined as a negative cough stress test with at least 300 ml bladder filling), UDI-6 score, operation time, morbidity, re-interventions and physical performance during recovery.
We hypothesized that the cure rate with MiniArc™ was non-inferior to the cure rate with Monarc™ and less painful. We needed 85 patients per group to have 90 % power to detect a drop in the lower bound of the confidence interval of cure from 90 % to 75 % using a one-sided test with α 0,025. We also would have 90 % power, with a two-sided test α 0,05, to detect a 20 % difference (8 points) in the VAS pain score. Anticipating that 10 % patients would not be evaluable we included 192 patients.

EXHIBIT HH

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ORIGINAL ARTICLE

Long-term follow-up of the retropubic tension-free vaginal tape procedure

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Abstract
Introduction and hypothesis Retropubic tension-free vaginal tape (TVT) was introduced in 1996 as a new and innovative surgical approach in the treatment of stress urinary incontinence (SUI). In this study we evaluate the long-term objective and subjective outcomes in a non-selected patient population 10 years after the retropubic TVT procedure.
Methods All women (603) operated on with retropubic TVT at four gynecological departments from September 1998 through December 2000 were identified, and those still alive (542) were invited to participate in this population-based prospective study. For subjective data a short-form urinary incontinence disease-specific questionnaire was used. For objective evaluation the women underwent a stress test. Data collected were merged with previously stored data in the Norwegian National Incontinence Registry Database.
Results We included 483 women; 327 attended a clinical follow-up consultation and 156 had a telephone interview. Median duration of follow-up was 129 months. Objective cure rate was 89.9 %, subjective cure rate was 76.1 %, and 82.6 % of the patients stated they were "very satisfied" with their surgery (treatment satisfaction rate). Only 2.3 % of the women had undergone repeat SUI surgery. Subjective voiding difficulties were reported by 22.8 %, the majority describing slow stream or intermittency. De novo urgency incontinence increased significantly from 4.1 % 6–12 months after surgery to 14.9 % at the 10-year follow-up.
Conclusions Long-term objective and subjective outcome after retropubic TVT is excellent with a low number of re-operations even in a non-selected cohort of patients.

Keywords Long-term follow-up · Mid-urethral slings · Stress urinary incontinence

Introduction

Retropubic tension-free vaginal tape (TVT) was introduced in 1996 as treatment for female stress urinary incontinence (SUI) [1]. Mid-urethral slings are currently considered the gold standard in the surgical treatment of SUI [2].

A significant rise in the prevalence of urinary incontinence among women was demonstrated in the United States (US) between 2001 and 2008 [3]. The US Food and Drug Administration (FDA) issued in 2011 a notification regarding serious complications associated with the use of transvaginal placement of synthetic meshes in pelvic organ prolapse (POP) surgery and is currently evaluating the use of surgical mesh in the treatment of SUI. As life expectancy increases and more women undergo incontinence procedures using mesh implants, it is of great importance to clarify long-term results and potentially unfavorable outcomes. The short-term results of TVT have been well documented, but few reports have published long-term data [4–8].

There is no consensus at present on how to define long-term follow-up after surgical procedures. A follow-up of

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5 years seems widely used, despite published examples of procedures demonstrating a decline in efficacy with time even after promising early results. As an example, a 14-year follow-up of Burch colposuspension, the previous gold standard in the surgical treatment of SUI, demonstrated a subjective cure rate of only 44 % combined with a high number of women stating voiding difficulties (36 %) [9].

The aim of our study was to evaluate objective and subjective results, re-operation rate for SUI, complications during and following surgery and potential long-term unfavorable outcomes in a non-selected cohort of women 10 years after retropubic TVT.

Materials and methods

This was a population-based prospective study of all women operated on with a retropubic TVT at four gynecological departments within the south-eastern region of Norway from 1 September 1998 to 31 December 2000. All these departments have reported their incontinence surgery data to the Norwegian National Incontinence Registry since its establishment on 1 September 1998 [10]. The majority of gynecological departments in Norway performing incontinence surgery report preoperative subjective and objective data, the type of incontinence procedures and complications, as well as 6–12 months' subjective and objective follow-up data to the National Incontinence Registry.

Tension-free vaginal tape from Gynecare, Ethicon was used, and the procedures were performed as described by Ulmsten et al. [1]. This non-selected patient population consisted of all the women who received TVT as either primary or recurrent surgical treatment for SUI, including those with urethral hypermobility, low urethral closure pressure or mixed urinary incontinence, as well as those undergoing concomitant POP surgery. Written consent for the long-term follow-up was obtained from all participants, the only exclusion criterion was inability to give such consent.

The Regional Committee for Medical and Health Research Ethics in south-eastern Norway deemed the study a quality assurance measure for treatment already established and therefore not in need of ethical approval outside the four departments. Approval was obtained from all department heads and institutional personal data officers.

All the women were invited to attend a 10-year clinical follow-up. Those unable to attend were asked to undergo a structured telephone interview for subjective data. The same short-form urinary incontinence disease-specific questionnaire was used for both categories [11]. The questionnaire has been validated in Norwegian and is used for preoperative, operative, 6- to 12-month routine data as well as for this study with 10-year postoperative data. The following non-validated supplemental questions were added for the 10-year follow-up:

1. How would you characterize the effect of the operation on your current leakage situation? (Choices given: "cured", "better", "unchanged" or "worse")
2. Have you had the feeling that it is difficult to empty your bladder after the operation? If yes, please describe in detail.
3. Has it been persistently painful to empty your bladder after the operation?

A stress test was performed before surgery and at subsequent follow-ups, including at the 10-year clinical follow-up. It consists of pad weighing after 20 jumping jacks on the spot and three forceful coughs in the standing position with 300 ml bladder volume. This stress test has been found to be reproducible [12]. Women unable to perform the test were asked to do a modified version consisting of 10 coughs in the standing position with 300 ml bladder volume. The women were considered objectively cured if the standard or modified stress tests were negative. Any change in pad weight (≥1 g) performing either stress test was considered a positive test and registered as an objective failure. Maximum flow rate (flowmetry) and post-void residual volume (catheter or bladder scanner) were recorded. The vagina was inspected in the semi-lithotomy position for asymptomatic tape exposure.

Primary objective outcomes were cure rate (defined as negative stress test or modified stress test), failure rate (defined as any leakage during the stress tests or the patient having undergone repeat SUI surgery) and re-operation rate (defined as repeat SUI surgery). Primary subjective outcomes were treatment satisfaction rate, cure rate, improved rate, and failure rate. The question on treatment satisfaction has been validated and contains the choices "very satisfied," "moderately satisfied," "neither satisfied nor dissatisfied," "moderately dissatisfied," and "very dissatisfied" [11]. Treatment satisfaction rate was defined as the percentage of women answering they were "very satisfied." Subjective cure rate was defined as the percentage of women answering "cured" on supplemental question 1, improved rate as "cured" or "better," and failure rate as "unchanged" or "worse." Secondary outcome measures were complications during or immediately following surgery recorded in the Registry Database and any long-term unfavorable outcomes discovered at the 10-year follow-up. The women were asked if they remembered any complications. In cases of discrepancy between this information and the patient's data recorded in the Registry Database, the patient's hospital medical records were reviewed. Long-term unfavorable outcomes that were investigated included objective voiding difficulties (maximum flow rate Q_{max}<15 ml/s, post void residuals>100 ml or>200 ml), vaginal mesh exposure, subjective voiding difficulties, recurrent urinary tract infections

(patients stating having received more than three treatments over the last 6 months), de novo urgency incontinence, and persistent painful voiding.

Women having undergone repeat SUI surgery (n=6 for objective data and n=11 for subjective data) were defined as TVT outcome failures when the primary objective outcomes were calculated. These women were excluded when the primary subjective outcomes and long-term unfavorable outcomes were calculated. All outcomes were calculated using per-protocol analysis. Thus, for each outcome variable the denominator was obtained by subtracting women with missing data from the total number of patients.

All participating women had subjective and objective preoperative, operative, and 6- to 12-month data stored in the National Registry Database. After merging the databases, a comparison of objective cure rates and treatment satisfaction rates was performed for the 6- to 12-month and 10-year follow-up data.

The validated questionnaire stratifies into stress- and mixed incontinence [11]. The stress incontinence index ranges from 0 to 12 and the urgency incontinence index from 0 to 8 [11]. In this study we defined de novo urgency incontinence as a woman with no preoperative symptoms of urgency incontinence (urgency incontinence index score=0) who developed postoperative urgency incontinence (urgency index score>0 combined with the need for pad use).

To evaluate whether women operated on in the study departments were representative of the national patient group, we compared the study group with the remaining women in the National Registry Database who had undergone a TVT operation in the same time period (n=747). The preoperative variables age, 24-hour pad test, stress test, post-void residual volume, maximum flow rate, maximum urethral closing pressure (MUCP), stress incontinence index score, and urgency incontinence index score were compared.

Methods, definitions, and units in this study conform to the standards recommended by the International Urogynecological Association and International Continence Society joint report on the terminology for female pelvic floor dysfunction [13].

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS-PC), version 15. Both categorical and continuous variables are reported as percentage, median, and range. Differences in dichotomous variables were tested using McNemar's test for paired variables and Pearson's Chi-Squared test for unpaired variables. Differences in continuous variables were tested using the Mann–Whitney U test. A significance level of 5 % was used.

Results

Recruitment and drop out of study participants is shown in Fig. 1. The 603 operations were performed by 21 surgeons. Median duration of follow-up was 129 months (range 114–160). Baseline characteristics are provided in Table 1 and primary outcome measures in Table 2.

Objective cure after 10 years was 89.9 %, and 2.3 % of the women had undergone repeat SUI surgery. Of the 11 patients (2.3 %) who had repeat SUI surgery, 9 received another TVT and 2 a bulking agent.

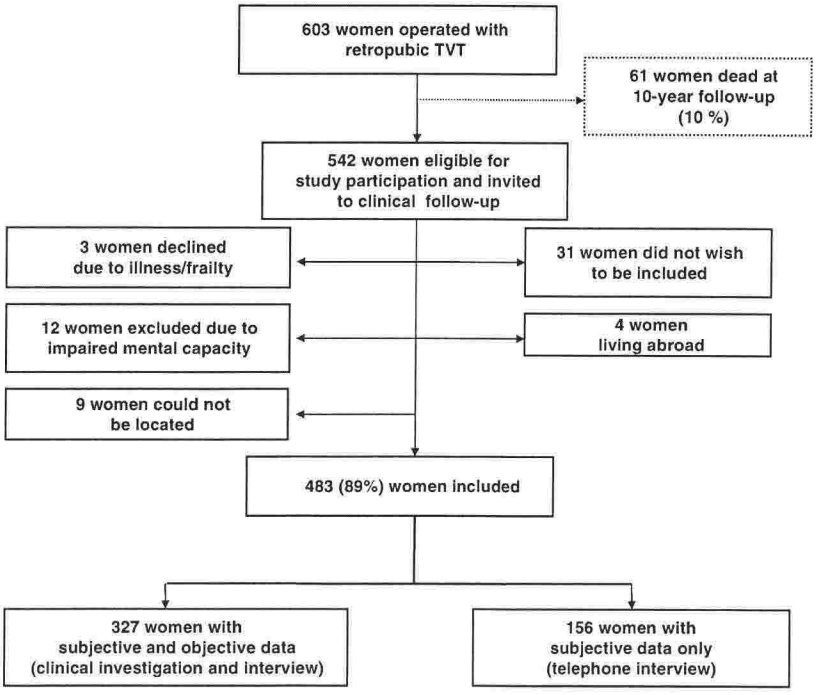

Fig. 1 Recruitment and drop-out of the study participants

Table 1 Baseline characteristics of the study participants at the 10-year follow-up (N=483)

Characteristics	
Demographics, median (range)	
Age (years)	64 (36–97)
BMI	26 (17–51)
Median time of follow-up (months)	129 (114–160)
Clinical characteristics, percentage (numbers/total/missing info)	
Topical estrogen use	16.7 (80/480/3)
Current smoking	21.7 (98/452/31)
Hysterectomy in the follow-up period	4.4 (21/482/1)
Pelvic organ prolapse surgery in the follow-up period	4.2 (20/481/2)
Current use of antimuscarinic medication	7.9 (38/481/2)

Primary subjective outcomes at the10-year follow-up were: 76.1 % cured, 18.0 % better, 3.4 % unchanged, and 2.5 % worse. The majority, 82.6 %, stated they were "very satisfied" with the operation.

Secondary outcomes are shown in Tables 3 and 4. Table 3 shows complications recorded during or immediately following surgery for a total complication rate of 8.7 %, the most common being hematomas of more than 4 cm in diameter.

Unfavorable long-term outcomes are shown in Table 4. Significantly more women had a low maximum flow rate and post-void residual above 100 ml at the 10-year follow-up compared with the preoperative data (Table 4). None had post-void residuals above 200 ml. There was an increase in de novo urgency incontinence from 6 to 12 months to 10 years post-surgery (4.1 % vs 14.9 %, p=0.01).

Subjective voiding difficulties were reported by 22.8 %, the most common being a slow stream or intermittency (Table 4). The percentage of women stating they were "very satisfied" with the treatment was similar for the women reporting voiding difficulties and those reporting no such problems (83.2 % vs 82.3 %, p=0.84). Furthermore, there was no difference in objectively low urinary flow (Q_{max}<15 ml/s) at the 10-year follow-up between the groups (27.7 % vs 27.1 %, p=0.92).

Only 1 case of asymptomatic mesh exposure was found at the 10-year follow-up. In addition, 3 mesh exposures had previously been recognized and surgically handled, bringing the total number of exposures to 4 (0.8 %) for the whole 10-year period. The surgical method used was excision of the exposed part of the tape and then re-suturing of the vaginal wall after mobilizing the edges of the defect.

This study revealed a small but significant decline in the percentage of women stating that they were "very satisfied" with the treatment from 6 to 12 months to 10 years post-surgery (89.1 % vs 82.6 %, p=0.006) despite no change in objective cure rates (90.2 % vs 89.9 %, Table 2).

Women stating that they were "very satisfied" had a significantly lower median urgency incontinence index score after 10 years compared with those not stating "very satisfied" (0 vs 5, p<0.001). Similar results were found when comparing women stating that they were "cured" after

Table 2 Primary objective and subjective outcome measures

Results	6–12 months Percentages (numbers/total/missing info)	10 years Percentages (numbers/total/missing info)	p value*
Objective results[a]	(N=327)	(N=327)	
Objective cure rate	90.2 (285/316/11)	89.9 (285/317/10)	0.86
Objective failure rate	9.8 (31/316/11)	10.1 (32/317/10)	0.86
	(N=483)	(N=483)	
Re-operation rate	0.6 (3/476/7)	2.3 (11/476/7)	0.008
Subjective results[b]	(N=480)	(N=472)	
Subjective cure rate	_[f]	76.1 (359/472/0)	
Subjective improved rate[c]	_[f]	94.1 (444/472/0)	
Subjective failure rate[d]	_[f]	5.9 (28/472/0)	
Treatment satisfaction rate[e]	89.1 (407/457/23)	82.6 (389/471/1)	0.006

*McNemar's test for paired variables

[a] Patients with repeat SUI surgery are classified as failures

[b] Patients with repeat SUI surgery are excluded

[c] Subjective improved rate defined as "cured" or "better"

[d] Subjective failure rate defined as "unchanged" or "worse"

[e] Percentage of women stating they were "very satisfied" with the treatment

[f] Subjective evaluation of the result was not part of the 6- to 12-month questionnaire and hence subjective cure rate, improved rate, and failure rate could not be calculated

Table 3 Secondary outcome measures I: complications registered during or immediately following surgery

Type of complications	Percentage (numbers/total/missing info)
Total	8.7 (42/483/0)
Hematoma (> 4 cm)	2.5 (12/483/0)
Superficial infection[a]	0.6 (3/483/0)
Deep infection[b]	0.8 (4/483/0)
Bladder perforations	1.2 (6/483/0)
Urethral injury	0.2 (1/483/0)
Bowel injury	0.0 (0/483/0)
Major vessel injury	0.0 (0/483/0)
Major bleeding (> 500 ml)	0.4 (2/483/0)
Catheterization>1 week	1.7 (8/483/0)
Catheterization>1 month	1.0 (5/483/0)
Postoperative vaginal mesh exposure	0.6 (3/479/4)
Postoperative sling release	1.9 (9/477/6)

[a] Local tenderness with redness and/or purulent discharge

[b] Abscess formation with or without sinus tract formation

10 years compared with those stating not "cured" (0 vs 4.5, $p<0.001$).

Patient characteristics of participating women operated on in the study departments differed from other TVT-operated women in the Registry Database only for the following preoperative variables: lower median post-void residuals (0 ml vs 5 ml, $p<0.001$), lower median MUCP (40 cm H_2O vs 45 cm H_2O, $p=0.03$), and higher median urgency incontinence index score (4 vs 3, $p<0.001$). There were no differences in median age, 24-hpad tests, stress tests, maximum flow rates or stress incontinence index scores.

Discussion

Our long-term follow-up study demonstrates an objective cure rate of 89.9 % after 10 years. This excellent result is in accordance with previous long-term follow-up studies of more selective and smaller study populations, reporting objective cure rates from 84 % to 93.1 % [4–8]. The subjective cure rate (76.1 %) in our study is also well within the 65–89.7 % range found by others [4–8]. The difference in objective and subjective cure rates found in our study (89.9 % vs 76.1 %) may be explained by de novo urgency incontinence symptoms. This assumption is based on our study demonstrating a significantly higher median 10-year urgency incontinence index score in the women stating that they were not cured compared with those stating that they were cured (score 4.5 vs 0, $p<0.001$). A similar difference was seen among women stating that they were "very satisfied" with their treatment compared with the others (score 0 vs 5, $p<0.001$).

We found the objective cure rate unchanged from 6 months to 10 years post-surgery ($p=0.86$, Table 2), in line with the publication by Serati et al. [5]. However, in contrast to Serati et al., who also showed stable subjective outcomes over a 10-year period, we found a small but significant decline in women stating that they were "very satisfied" from 6 months to 10 years post-surgery ($p=0.006$, Table 2) [5]. Given the heterogeneous nature of our patient population we still think it satisfactory that as many as 82.6 % state that they are "very satisfied" with the surgery given 10 years earlier; this is also higher than the 74 % demonstrated by Olsson et al. [6]. The subjective cure rate and treatment satisfaction rate found in our non-selected patient cohort 10 years after surgery are also encouraging compared with the 44 % cure rate14 years after Burch colposuspension [9].

The present study revealed a 4.2 % incidence of subsequent pelvic organ prolapse (POP) surgery after TVT (Table 1). The occurrence and development of POP have in the past been associated with Burch colposuspension [9, 14], but to a lesser degree with TVT [15]. Our finding of 4.2 % of patients having undergone subsequent POP surgery during follow-up after TVT may therefore add some insight into this potential association, but must not be mistaken for the true post-TVT incidence of POP, since our study was not designed to systematically evaluate persistent or de novo pelvic organ prolapse beyond recording any subsequent POP surgery.

Our study illustrates the difficulties encountered when evaluating long-term results in an ageing population. Recurrence of stress incontinence as well as recurrence or occurrence of POP, urgency, and urgency incontinence over time could be interpreted both as consequences of the surgical procedure 10 years previously as well as the effects of normal deterioration of the pelvic floor function caused by advancing age. The prevalence of urgency incontinence symptoms [16–19] and pelvic organ prolapse [20] are both known to increase with age . We have no comparable group of non-operated women followed over the same time period in order to control for age-associated incontinence symptoms.

It is well known that TVT may lead to bladder outlet obstruction [21]. We found a high number of women reporting voiding difficulties after 10 years, the majority complaining of a slow or intermittent urine stream (Table 4). However, the "very satisfied" rates were almost identical among those with and without subjective voiding problems (83.2 % vs 82.3 %, $p=0.84$) and there was no differences in objectively low urinary flow ($Q_{max}<15$ ml/s) between the groups (27.7 % vs 27.1 %, $p=0.92$). We therefore consider it unlikely that the reported voiding difficulty represents a serious clinical problem for these women at the present time.

Table 4 Secondary outcome measures II: unfavorable long-term outcomes[a]

	Percentage (numbers/total/missing info)		p value [c]
Objective voiding difficulties (among n=321)			
	Preoperative	10 years	
Q_{max}<15 ml/s	11.0 (18/164/157)	26.7 (79/296/25)	<0.001
Post-void residuals>100 ml	0.3 (1/310/11)	3.5 (11/313/8)	0.006
Post-void residuals>200 ml	0.0 (0/310/11)	0.0 (0/313/8)	
	At 6–12 months	10 years	
Q_{max}<15 ml/s	Incomplete data	26.7 (79/296/25)	
Post void residuals>100 ml	0.7 (2/306/15)	3.5 (11/313/8)	0.039
Asymptomatic vaginal mesh exposure (among n=321)		0.3 (1/317/4)	
Subjective voiding difficulties (among n=472)		22.8 (107/469/3)	
The 107 patients who reported voiding difficulties were categorized into the following groups			
A: Slow stream or intermittency		43.1 (44/102/5)	
B: Position-dependent micturition		5.9 (6/102/5)	
C: Need to immediately re-void		11.8 (12/102/5)	
D: Feeling of incomplete bladder emptying		7.8 (8/102/5)	
E: Straining to void		9.8 (10/102/5)	
F: Hesitancy		4.9 (5/102/5)	
G: More than one of the above		7.8 (8/102/5)	
H: Other		8.8 (9/102/5)	
Recurrent urinary tract infections (among n=472)		2.3 (11/471/1)	
Persistent painful voiding (among n=472)		1.1 (5/469/3)	
De novo urgency incontinence (among n=101)[b]			
	6–12 months	10 years	
	4.1 (4/98/3)	14.9 (15/101/0)	0.013

[a] For the evaluation of true 10-year secondary outcome measures the 11 re-operated patients were excluded (6 with objective data and 11 with subjective data)

[b] De novo urgency incontinence defined as postoperative urgency incontinence index >0 and having to use pads (among n=101 with preoperative urgency incontinence index =0)

[c] McNemar's test for paired variables

The low number of patients with post-void residuals above 100 at the 6- to 12-month evaluation also indicates that the voiding difficulties found at 10 years are more likely due to ageing than procedure-related. However, since no voiding cystometry was performed, we cannot exclude partial obstruction developing over time with compensatory increased detrusor pressure coexisting with normal flow and absence of post-void residuals in these patients. Further ageing could then theoretically cause these patients to experience increasing voiding difficulties in the future. Very few patients had objectively impaired voiding as assessed by high post-void residuals and/or low maximum flow rates (Table 4). In our study, 3.5 % of the women had post-void residuals above 100 ml at the 10-year clinical follow-up, which is a significant increase from the 0.3 % of women with a residual above 100 ml recorded before surgery and from the 0.7 % recorded at the 6- to 12-month follow-up (Table 4). However, only one of the women with high post-void residuals reported recurrent urinary tract infections. Also, an overestimation of post-void residuals may have occurred, since the women were examined only once and repeat measurement has been shown to produce lower volumes [22].

The large number of women included strengthens the results in this follow-up study. The use of a national registry removes the risk of selection bias that may occur when patient cohorts with specific inclusion and exclusion criteria are recruited to observational or randomized, controlled trials. Also, our national database better evaluates surgical outcomes in the routine clinical setting, as multiple surgeons with different levels of training perform the TVT procedures.

Another advantage of our study is that only high-volume TVT surgery departments participated, as variations in operating volumes have been shown to influence patient outcome [23].

The significantly lower median preoperative MUCP (40 vs 45 cm, p=0.03) and higher median preoperative urgency incontinence index score (4 vs 3, p<0.001) in our study compared with the other women in the national registry database further strengthens our results, as both a low

MUCP and mixed incontinence are associated with poorer outcomes [24, 25].

Our study has some limitations, including loss to follow-up (11 %), as lost patients can be interpreted as failures and therefore influence cure rates [26]. In our study few women were lost to follow-up. Being offered an opportunity for clinical evaluation would presumably be a strong motivation for women with failed surgery or dissatisfaction to join the study. We therefore think it unlikely that the women refusing participation were more dissatisfied with the TVT procedure than those agreeing to participate.

For this 10-year study, three supplemental, non-validated questions were added to the standard national follow-up questionnaire [11]. The questionnaire also lacked a question exploring de novo urgency without incontinence. However, 14.9 % of women reported de novo urgency incontinence in our study, and this is in accordance with de novo urgency incontinence rates of 1–17 % found after TVT in other publications [7, 27, 28].

Another weakness of our study could be that use of registry data includes the possibility of inaccuracies in the individual entries and the results must therefore always be interpreted with this in mind.

In conclusion, our study demonstrates excellent objective and subjective outcomes and a low number of re-operations in a non-selected cohort of women 10 years after retropubic TVT. The fact that these outcomes are found even when numerous surgeons have performed the operations, illustrates the robust properties of the procedure. The small but significant decline in treatment satisfaction 10 years after surgery, despite no difference in objective cure rates may be explained by an increase in urgency incontinence symptoms caused by advancing age.

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EXHIBIT II

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Acta Obstetricia et Gynecologica Scandinavica

ORIGINAL ARTICLE

Long-term efficacy of Burch colposuspension: a 14-year follow-up study

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Background. The aim of this study is to investigate the long-term efficacy of the Burch colposuspension and to analyze the risk factors for an unsuccessful outcome at the long-term follow-up of more than 10 years.
Methods. Data from patient files of 190 women on whom surgery was performed with Burch colposuspension during 1980–1988 and answers from a postal questionnaire performed median 14 years after the Burch colposuspension concerning the lower urinary tract function were retrieved retrospectively.
Results. Subjectively significant urinary incontinence was experienced by 56% of the responders. Only 19% reported no incontinence episodes. Among the significant urinary incontinent women, symptoms of stress incontinence occurred in 26%, urge incontinence in 17%, and mixed incontinence in 42%. In 15%, the symptom of incontinence was atypical and could not be categorized. Feeling of incomplete bladder emptying post-operatively and pre-operative obesity was associated with the long-term outcome of Burch colposuspension (odds ratio (OR) = 2.33; 95% confidence interval (95% CI) = 1.20–4.54 and OR = 2.52; 95% CI = 1.10–5.77, respectively). Age, obesity at the long-term follow-up or having had surgery for fecal incontinence, genital prolapse, or hysterectomy were not significantly associated with the outcome of the Burch colposuspension.
Conclusions. The subjective cure rate decreases with time after Burch colposuspension. Lower urinary tract symptoms are very common at the long-term after Burch colposuspension with more than three-fourth experiencing these. Feeling of incomplete bladder emptying post-operatively and pre-operative obesity seem to be long-term risk factors for an adverse outcome. A standard definition for follow-up periods is suggested.

Key words: Burch colposuspension; cure rate; long-term follow-up; risk factor; urinary incontinence

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The mean age of women who undergo surgery for stress urinary incontinence (SUI) is about 50 years (1–3). Because the expected lifetime of women is more than 75 years in most western countries, these women may be assumed to live more than 25 years after the surgery. The first surgery is the most successful one and recurrent surgeries show lower cure rates (3,4). This emphasizes the importance of long-term durability of the first surgical procedure.

Burch colposuspension is considered as one of the most effective surgeries for the treatment for genuine SUI (5,6). The method is, however, encumbered with a significant post-operative morbidity, such as an increased occurrence of voiding difficulties and genital prolapse (3,7–10). The long-term result concerning continence even seems to decrease with time (11–13). Thus, possible risk factors for an adverse outcome may change with time.

Abbreviations:
BMI: body mass index; BSO: bilateral salpingo-oophorectomy; DIS: detrusor instability score; SUI: stress urinary incontinence; UTI: urinary tract infection.

The aim of the present study is to investigate the long-term efficacy of the Burch colposuspension and to analyze the risk factors for an unsuccessful outcome at the long-term follow-up of more than 10 years.

Patients and methods

The 243 patients with SUI operated upon with the Burch colposuspension at our department during 1980–1988 have previously been described in detail (3). Seven had died at the 6-year follow-up and four did not answer the questionnaire in 1990. Of the remaining 232 women, 12 were deceased in 1998, thus 220 were accessible for the present study. The patient files were retrieved and information concerning preoperative length and weight of the patient, per-operative bleeding volume, and clinical competence of the surgeon (senior consultant, consultant, senior registrar, registrar) was registered.

In November 1998, a postal questionnaire was sent to all patients alive. The postal questionnaire consisted of 66 questions concerning the symptoms of pelvic floor dysfunction, pregnancies, childbirths, gynecologic surgery, general health and demographics. The questions were selected from published questionnaires concerning the urinary and bowel functions (14,15). Twenty-six questions concerned the bowel function (15). The result of these questions is outside the scope of this study; thus, it has not been reported in this study. Nineteen questions were about the lower urinary tract function (14). Ten of these questions were modified from the Detrusor Instability Score (DIS) developed by Kauppila et al. (16) and were only answered by the women who stated that they then had urinary incontinence.

The incontinence was categorized according to the answers of the questions concerning the occurrence of incontinence at physical activity/exertion or at urge as stress incontinence or urge incontinence. Mixed incontinence was defined as incontinence when the patient exhibited symptoms of both stress and urge incontinence.

The options for answers of the questions in the questionnaire were operationalized to a limited number of box-alternatives or to specification of a number. The question concerning the occurrence of urinary incontinence was answered giving the frequency of incontinence episodes in: never; a few times per year; a few times monthly; a few times weekly, or daily episodes of incontinence. The type of daily working activity was stated on a three-grade scale as: light, quiet, mostly sitting work; much physical activity, but no physical heavy lifting; and heavy work with daily heavy lifting.

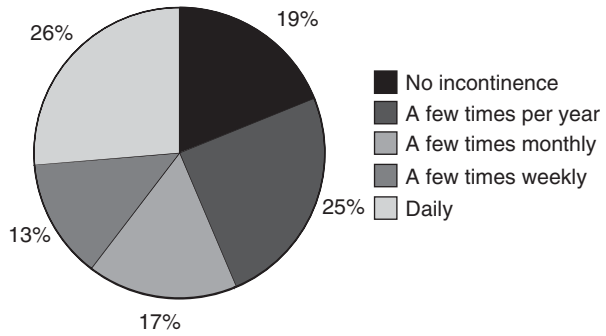

Fig. 1. Distribution of the occurrence of urinary incontinence median 14 years after Burch colposuspension in 190 women.

The occurrence of incontinence was dichotomized and leakage that occurred with a frequency of monthly or more often was considered as significant incontinence.

The non-responders received a reminding letter with a questionnaire within 3 weeks after the first letter. No further contact was established if the person did not respond after that letter.

The study was approved by the Ethical Research Committee of the Medical Faculty of Linköping University, Sweden.

Statistics

The data have been presented as numbers and frequencies or median and range. The results were analyzed statistically by means of non-parametrical statistics. Mann–Whitney *U*-test and Kruskal–Wallis test were used, when appropriate. In the analyses of associations between urinary incontinent and continent women, the Mantel-Haenszel technique for the determination of odds ratio (OR) and 95% confidence interval (CI) was used. A P-value of <0.05 was considered significant.

Results

The response rate of the postal questionnaire was 87% (192/220). The one hundred ninety women who answered the question concerning the occurrence of urinary incontinence made up the study group. The median follow-up period was 14.0 years (range: 10–18).

Subjectively significant urinary incontinence was observed in 56% (107/190) median 14 years (range: 10–18) after the Burch colposuspension. The frequency distribution of the occurrence of urinary incontinence has been demonstrated in Fig. 1. In the group with significant urinary incontinence, the symptoms of stress incontinence, urge incontinence, or mixed incontinence were found in 26, 17, and 42%, respectively. In 15%, the symptoms were atypical and the urinary incontinence could not be categorized as stress, urge, or mixed incontinence.

At least one of the symptoms of voiding problems – difficulty in starting voiding, straining at voiding, or feeling of incomplete emptying of the bladder – occurred in 36% (69/190). Difficulties in starting voiding were reported in 12%, straining at voiding in 11%, and difficulties in emptying the urinary bladder in 30%. In the incontinent women, recurrent lower urinary tract infections (UTI) three times or more per year occurred in 10%. Only those who reported any urinary incontinence answered the questions concerning the DIS. Of the 154 with any urinary incontinence, 109 completed these questions. The median DIS was 9 (range: 3–16) among those who were categorized as having significant urinary incontinence, and also 9 (range: 5–13) among those with subjectively non-significant urinary incontinence.

The difference in DIS was not statistically significant.

According to the body mass index (BMI), 19% were classified as obese (BMI $\geq$30 kg/m^2) at the time of the surgery and 35% had overweight (BMI $\geq$25 and $<$30). At the follow-up, 21% were classified as obese and 42% as having overweight.

Twenty surgeons performed the surgeries. Six of the surgeons performed 70% of the surgeries. The senior consultants performed surgery on 13% of the patients; the consultants performed surgery on 12%; the senior registrars performed surgery on 69%, and the registrars performed surgery on 6%. No significant difference was found in cure rate between the various categories of surgeons.

The median per-operative bleeding was 200 ml (range: 50–2400). The consultants and registrars had significantly larger per-operative bleedings, compared to the senior consultants and senior registrars (median: 300, 275, 150, and 200 ml, respectively; Kruskal–Wallis test; $P = 0.018$). Ten of the patients had per-operative bleeding of $\geq$1000 ml. There were no significant differences in per-operative bleeding volume or the number of patients with bleeding of $\geq$1000 ml between the continent and the incontinent at the long-term follow-up.

Concomitant gynecologic surgery at the Burch colposuspension was performed in 19 patients (10%): total abdominal hysterectomy with or without salpingo-oophorectomy (BSO) was performed in 10 patients (5.2%); subtotal abdominal hysterectomy with or without BSO in three patients (1.5%); ovarian resection in two patients (1%); closure of the pouch of Douglas ad modum Moschowitz in one patient (0.5%); posterior colporrhaphy in three patients (1.5%). At the time of the follow-up, 37% in all had had surgery for genital prolapse, 29% had undergone hysterectomy, 12% had had BSO, and fecal incontinence surgery had been performed in 3%.

The associations between possible risk factors and the occurrence of significant urinary incontinence have been shown in Tables I–III. The follow-up period was similar – 14.0 years (range: 10–18) for the significant incontinent women and the continent women.

Pre-operative obesity (BMI $\geq$ 30) was strongly associated with the outcome of the surgery at the long-term follow-up. At the 6-year follow–up, this association was not significant (OR = 1.77; 95% CI = 0.84–3.75). The older age groups ($\geq$60 years at the time of the surgery) demonstrated lower cure rates, but not significantly. Hysterectomy, surgery for genital prolapse, or fecal incontinence did not seem to be associated with the long-term efficacy concerning urinary continence. The associations between voiding problems and urinary incontinence seemed to withstand even at the long-term follow-up. The occurrence of at least one of the three symptoms of voiding dysfunction was significantly more often seen in the group with subjectively significant urinary incontinence than that among the non-significant incontinent women. Of the three symptoms of voiding problems investigated, only difficulty in emptying the urinary bladder was statistically and significantly more common in the incontinent group. Comparing the occurrence of at least one of the voiding dysfunction symptoms between those with urinary leakage of any frequency and those who were completely continent after the colposuspension at the long-term follow-up showed a stronger association with an OR of 13.1; 95% CI = 3.04–56.4. Each of the three symptoms did show significant associations

Table I. Associations between the demographic and obstetric data and the occurrence of significant urinary incontinence median 14 years after Burch colposuspension

	Urinary incontinent women $n = 107$ (%)	Urinary continent women $n = 83$ (%)	*P*-value or OR (95% CI)
Age at surgery (years)	49.0 (28.2–75.1)	48.0 (30.8–71.7)	Not significant
Age $\geq$60 years at surgery	19 (18)	9 (11)	1.78 (0.76–4.16)
Estrogen treatment at present*	68 (63)	42 (51)	1.70 (0.95–3.05)
Heavy work load	45 (43)	31 (35)	1.38 (0.77–2.47)
Body mass index (BMI) at surgery (kg/m^2)	25.8 (18.5–36.6)	24.5 (19.5–38.3)	Not significant
BMI of $\geq$30	25/99 (25)	9/76 (12)	2.52 (1.10–5.77)
BMI at follow-up (kg/m^2)	26.6 (19.6–38.6)	25.7 (18.8–37.2)	Not significant
BMI of $\geq$30	25/103 (24)	12/79 (15)	1.79 (0.84–3.83)
Parity	2.0 (0–8)	2.0 (0–7)	Not significant
Nulliparous	3 (2.8)	3 (3.6)	0.77 (0.15–3.91)
Mode of delivery			
Normal vaginal deliveries	93 (89)	71 (89)	1.07 (0.42–2.73)
All other modes	11 (11)	9 (11)	
Large perineal lacerations or episiotomy	13 (13)	9 (12)	1.19 (0.42–2.94)

*Estrogen treatment includes local and systemic treatment.

Table II. Associations between the clinical data and the occurrence of significant urinary incontinence median 14 years after Burch colposuspension

	Urinary incontinent women $n=107$ (%)	Urinary continent women $n=83$ (%)	*P*-value or OR (95% CI)
Hysterectomy at anytime	34 (32)	22 (27)	1.29 (0.68–2.44)
Before Burch colposuspension	8 (7)	6 (6)	1.26 (0.40–4.00)
Concomitant to Burch colposuspension	9 (8)	4 (5)	1.80 (0.54–6.11)
Subsequent to Burch colposuspension	17 (16)	13 (16)	1.02 (0.46–2.23)
Genital prolapse surgery at anytime	38 (36)	32 (39)	0.88 (0.48–1.59)
Before Burch colposuspension	3 (3)	4 (5)	0.57 (0.12–2.62)
Concomitant to Burch colposuspension	3 (3)	0 (0)	Not significant
Subsequent to Burch colposuspension	32 (30)	28 (34)	0.84 (0.45–1.55)
Fecal incontinence surgery	5 (4.7)	1 (1.2)	4.02 (0.46–35.1)

when comparing those with urinary incontinence of any frequency with those who were completely continent (data not shown). In all women with incontinence of any frequency, recurrent UTI occurred in 14% of the women with voiding problems and in 8% of those without voiding problems (OR = 1.78; 95% CI = 0.63–5.07).

Discussion

Follow-up studies concerning anti-incontinence surgery often consider 3–5 years as long-term (1–3). This time period is probably too small, because the recurrence rate usually increases with time (3,11–13,17). Thus, in order to disclose the risk factors, real long-term follow-up is necessary. The established risk factors at the short-term follow-up may change with time. There is no general accepted standard by the international community, i.e. the International Continence Society or the International Urogynecological Association, of what is long-term follow-up in urogynecology. This should be considered in the international urogynecologic society in order to obtain correct comparisons of the outcome of treatments. In pelvic floor reconstructive surgery, any follow-up period of less than 5 years should be noted as short-term follow-up, a follow-up period of 5–10 years as a medium-term follow-up, and a follow-up period of 10 years or more should be noted as long-term follow-up.

The present long-term follow-up study of the Burch colposuspension demonstrates a deterioration of the continence rate with time. In the previously published 6-year follow-up study (3), the subjective continence rate was 63%, compared to the 44%, 14 years after the Burch colposuspension. Alcalay et al. (11) found that the cure of incontinence following Burch colposuspension was time-dependent, with a decline for 10–12 years when a plateau was reached. The results of our study are comparable with those of other long-term studies of the Burch colposuspension (1,11,13,17).

Voiding difficulties have been reported to be a major concern after Burch colposuspension occurring in 22–32% even at the long-term (3,7,11). Compared to our 6-year follow-up study (3), the occurrence of voiding difficulties seemed to remain unchanged at the 14-year follow-up. Lose et al. (7) found approximately 40% with stranguria, i.e. a symptom of voiding dysfunction 26 months after the surgery. The present study confirms that the significant morbidity of voiding problems after Burch colposuspension persists at the long-term with 36% having the feeling of incomplete bladder emptying.

As reflected in the high DIS found in the incontinent group, a large proportion of the women with significant urinary incontinence after Burch colposuspension had the symptoms of urgency and urge incontinence (59% – urge incontinence 17% + mixed incontinence 42%), which has also been reported by other authors (7,11,13,18,19). Subjectively *de novo* urge symptoms occurred in 36%. This emphasizes the statement by Sand and co-workers that patients undergoing Burch colposuspension should understand the possibility

Table III. Associations between voiding problems and the occurrence of significant urinary incontinence median 14 years after Burch colposuspension

	Urinary incontinent women $n=107$ (%)	Urinary continent women $n=83$ (%)	OR (95% CI)
At least one symptom of voiding dysfunction	46/107 (43)	23/83 (28)	1.97 (1.06–3.64)
Difficulties in starting voiding	15/105 (14)	8/81 (10)	1.52 (0.61–3.79)
Straining at voiding	13/105(12)	7/81 (9)	1.49 (0.57–3.93)
Difficulties of emptying the bladder	39/103 (38)	17/82 (21)	2.33 (1.20–4.54)

that the surgery may cause urinary incontinence because of detrusor instability even if it cures their genuine stress incontinence and that if they have both genuine stress incontinence and detrusor instability their chances for an operative cure of both conditions are low (19).

The occurrence of recurrent UTI seemed to decrease. In the 6-year follow-up, it was 16% among the patients with incontinence (3); at the 14-year follow-up, it was 10%. Lose et al. (7) found UTI in 29% of all at the follow-up mean of 26 months, whereas Alcalay et al. (11) reported recurrent UTI in 5% in their 10–20 year follow-up study.

The occurrence and the development of genital prolapse have been associated with Burch colposuspension (9,10,13). Kwon et al. recently published a study that questioned this association (20). They found that genital prolapse did not occur later on in those women who pre-operatively did not have a prolapse. The dropout rate in their study was 43% and the examination used pre-operatively and post-operatively was, however, not uniform and thus the results were uncertain. In the present study, genital prolapse surgery had been performed in 37% of the patients at the long-term follow-up. In the study by Alcalay et al., 30% had had a prolapse surgery before the colposuspension and afterward 26% had a posterior repair and 5% an enterocele repair (11). The association between the outcome of colposuspension and the occurrence of genital prolapse is unclear. We have previously reported that genital prolapse occurs significantly more often in the group of incontinent women after Burch colposuspension (9). But when it comes to genital prolapse that demands surgery this seems not to hold through. In the present study, the OR for genital prolapse surgery demonstrated a higher risk of prolapse surgery in the continent group than that in the incontinent group, although not significant.

The reports on the influence of hysterectomy on the outcome of the Burch colposuspension are conflicting. However, often the association has been made with hysterectomy performed before or concomitant to the colposuspension surgery (21,22). If pelvic floor neuropathy caused by the hysterectomy is the etiology of urinary incontinence as suggested by Parys et al. (23) and Benson and McClellan (24), it seems more appropriate to determine the outcome of the colposuspension in relation to whether a hysterectomy has been performed or not at the time of the follow-up. This has been performed in the present study. Twenty-nine percent had had a hysterectomy. No significant difference was found in the incidence of having undergone hysterectomy between the significant urinary incontinent and continent women after Burch colposuspension at the long-term follow-up. The time of the executions of the hysterectomy in relation to the colposuspension did not seem to influence the outcome of the colposuspension either.

Controversy about the influence of the age at surgery for an adverse outcome of the Burch colposuspension exists (3,21,25,26). We found no significant difference in the outcome concerning continence in any particular age group. In our previous study (3), there was a trend for a lower cure rate for women older than 64 years at surgery. However, owing to the small number of remaining living patients from this age group, the results are not shown specifically for the age group of $\geq$65 years.

Obesity (i.e. BMI of $\geq$30 kg/m^2) at the time of the surgery was strongly associated with the outcome of the colposuspension at the long-term follow-up. The obese women had an increased risk of an adverse outcome of the surgery, compared to non-obese women. This is in accordance with other studies (11,27). Alcalay et al. (11), however, did only report the weight of the patient, which seems insufficient when describing obesity. On the contrary, Zivkovic et al. (28) reported no significant influence of the BMI on the outcome after Burch colposuspension, but their report was small with a low statistical power. The question is: What impact may weight reduction pre-operative have on the outcome of the colposuspension? No studies have been performed with this goal.

In the present study, BMI increased between the surgery and the follow-up in both groups. Thus, it seems that the weight increase after the surgery *per se* does not influence the outcome of the surgery.

Conclusions

This study demonstrates that the symptoms of lower urinary tract dysfunction are common at long-term follow-up, median 14 years after Burch colposuspension. Only 19% claim that they were completely continent. In 25%, the incontinence episodes occurred only a few times per year and 56% experienced significant urinary leakage monthly or more often. Symptoms of SUI occurred in 68% of those with significant leakage and urge incontinence was almost as common, occurring in 59%. The cure rate of the Burch colposuspension seemed to decline over time. Pre-operative BMI and post-operative

feeling of incomplete bladder emptying seem to be associated with the long-term symptom of urinary incontinence after the colposuspension. An international standard for definitions of follow-up is wanted and is suggested. The new minimal invasive techniques for surgical treatment for SUI seem promising concerning the cure rate as well as morbidity. However, no long-term studies (≥10-year follow-up) have been published.

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